UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE CIENCIAS QUÍMICAS

TESIS DOCTORAL

Estudio de la reactividad de sistemas insaturados frente a zwitteriones tipo koshar. Aplicaciones sintéticas

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Carlos Lázaro Milla

Directores

Benito Alcaide Alañón
Pedro Almendros Requena

Madrid

UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE CIENCIAS QUÍMICAS

Departamento de Química Orgánica I

ESTUDIO DE LA REACTIVIDAD DE SISTEMAS INSATURADOS FRENTE A ZWITTERIONES TIPO KOSHAR. APLICACIONES SINTÉTICAS

TESIS DOCTORAL

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Madrid, 2019

UNIVERSIDAD COMPLUTENSE MADRID

DECLARACIÓN DE AUTORÍA Y ORIGINALIDAD DE LA TESIS PRESENTADA PARA OBTENER EL TÍTULO DE DOCTOR

D./Dña. Carlos Lázaro Milla,
estudiante en el Programa de Doctorado en Química Orgánica,
de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid, como autor/a de la tesis presentada para la obtención del título de Doctor y titulada:

ESTUDIO DE LA REACTIVIDAD DE SISTEMAS INSATURADOS FRENTE A ZWITTERIONES TIPO KOSHAR. APLICACIONES SINTÉTICAS

y dirigida por: Benito Alcaide Alañón y Pedro Almendros Requena

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Esta DECLARACIÓN DE AUTORÍA Y ORIGINALIDAD debe ser insertada en la primera página de la tesis presentada para la obtención del título de Doctor.

A mi familia

“La vida es una reacción química que sólo requiere de equilibrio.”

(Priyavrat Gupta)

El trabajo recogido en esta Memoria forma parte de proyectos de investigación financiados por el MINECO y FEDER (CTQ2012-33664-C02-01, CTQ2012-33664-C02-02, CTQ2013-44303-P, CTQ2015-65060-C2-1-P y CTQ2015-65060-C2-2-P); y se ha realizado gracias a la concesión de una beca FPI del MINECO, organismo al que deseo expresar mi agradecimiento.

Bien, una vez hecha la pelota a los organismos que sueltan la guita (aunque se podían estirar un poco más, la verdad) pasemos a las personas humanas con pensamientos mentales.

Hace tiempo vi de casualidad la cita de un libro, *Orgullo y Prejuicio* de Jane Austen, que decía lo siguiente: “A muy poca gente quiero de verdad, y de muy pocos tengo buen concepto. Cuanto más conozco el mundo, más me desagrada, y el tiempo me confirma mi creencia en la inconsistencia del carácter humano y en lo poco que se puede fiar uno de las apariencias de bondad o inteligencia”. De manera demoledora y en cuatro líneas quedaba definido un sentimiento que se ha ido forjando en mi a medida que crecía. Sin embargo, no penséis que soy un cenizo amargado, no todo es tan negro y trágico como pueda parecer, pues a la primera frase de la cita yo le añadiría al final “…pero haberlos haylos” y ¡allá van unos cuantos!:

Sin duda, el primer agradecimiento tiene que ir dirigido a mi familia en general, a los que dedico esta Memoria, pero en particular a mis padres. Siento la falta de originalidad, pero es un sentimiento compartido por la mayoría que nuestros padres lo son todo para nosotros durante toda nuestra/su vida. Cuidadores, protectores, benefactores, apoyadores, mecenas y también, toca pelotas, pero luego te das cuenta que hacen lo correcto. Hablando de toca pelotas, mi hermana, esta es experta, es capaz de calentarme la cabeza como la tetera de una sorda en tiempo record. Sin embargo, eso es solo porque somos muy diferentes en nuestra manera de ser pero lo importante es que siempre está ahí si necesito algo y nos queremos mucho, a nuestra manera, pero mucho. No tuve oportunidad de conocer a mis abuelos, pero me lo han compensado con dos abuelas muy longevas con salud de hierro que siempre me han mimado, consentido y perdonado que no les dedique todo el tiempo que se merecen.

En cuanto a la gente del curro, quería agradecer a mis directores, Benito y Pedro, el tiempo, la dedicación y los recursos invertidos en mí. Particularmente agradecerles la libertad que siempre me han dado, pues básicamente durante estos años me han dejado hacer lo que me ha dado la gana (investigacionalmente

hablando) lo que me ha permitido aprender y trabajar muy a gusto, dando lo mejor de mí. También estoy muy agradecido a Amparo, Cristina, Teresa, Pilar y Sara, pues de todas ellas he necesitado algo durante todos estos años y siempre me han facilitado la vida sin poner una sola mala cara.

Tere Quirós y Gonzalo, de los que todos mis compis de laboratorio me han oído hablar como si de seres de luz se trataran, pues de ellos solo guardo buenos recuerdos. Tere, la combinación perfecta de persona culta, inteligente, trabajadora y buena gente, mi mentora en el laboratorio cuando apenas tenia idea de nada, me enseñó casi todo lo que hay que saber para trabajar en un laboratorio con una paciencia infinita, el ejemplo a seguir sin duda. Gonzalo, el bolo más grande que ha dado los Navalucillos, para España y el mundo. Un apoyo mutuo en el lab, con el humor infinito y Juan Luis Guerra siempre presentes, creo que con nadie me he reído más que contigo, un don poco común que me encanta. Un gran libro abierto sobre atajos y trucos en los procesos experimentales y de historias y anécdotas en el mundo rural. Un gran corazón y un gran amigo para toda la vida.

Pasando a otra persona y modificando un poco la frase de un hombre cuyo nombre esta codificado en clave, M. Rajoy: “los asturianos muy asturianos y mucho asturianos”. Esta frase define a Eduardo (es asturiano, por cierto, siempre de Oviedo, nunca de Gijón), un tipo currante, resolutivo y sidrero profesional, un placer trabajar codo con codo contigo y con el deseo de volver a hacerlo algún día.

Por supuesto no me olvido de mis correligionarios, gente que empezaron como compañeros de laboratorio o del grupo de investigación pero que ahora son amigos de verdad. Fernando, tranquilo y sosegado, un queda bien de libro, el hijo que nunca acabo de criar, siempre te digo que no me das más que disgustos, pero sabes que no es verdad y la balanza siempre la revientas hacia el lado de las cosas buenas, gran amigo, mejor persona y legítimo heredero de laboratorio. Mireia, debe ser lo más parecido a que te toque la lotería, no conozco a nadie que anteponga siempre a los demás antes que a sí misma como lo haces tú, trabajadora incansable, una persona que sabe ver la belleza ajena, incluso, y eso es lo más especial, en aquellos incapaces de percibir su propia belleza. Sin tu esfuerzo y dedicación junto a Cristina, no podría haber completado uno de los Capítulos de esta Tesis. Irene, orden y mando, sin paños calientes, cuando algo ha de hacerse se hace sin contemplaciones ni tonterías, eso me encanta de ti, podrías ser la Agustina de Aragón o la María Pita de nuestro tiempo, no me cabe duda.

También quiero agradecer la estancia de nuestra invitada helenística, Agathi, demostrando lo mal que se me da el inglés y lo poco que se necesita si dos personas quieren entenderse. Tampoco me olvido de todas aquellas personas que han pasado por el lab durante estos años para completar sus TFG y TFM, Nigar, Miriam, José, Roberto, Laura, David, Guille, Alejandro, Borja, Imanol, Ana, Miguelón, Miguel, Jon y Hristo. También Chimbo que, aunque no era de nuestro grupo, actuaba como tal. Si me dejo a alguien que no se moleste, ya se me olvidan los nombres.

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Para el final, pero no menos importantes, quería agradecer a todos los amigos/as de fuera del mundillo de la Tesis pero que a su manera también me han ayudado a completar la tarea. A Marta, la de El Espinar (aunque me gusta decirle de San Rafael para fastidiarla), uña y carne, gracias por compartir tantos momentos conmigo, largas conversaciones, venturas y desventuras, apoyo mutuo y psicoterapeuta clandestina. Andrea, alegre, simpática, divertida, avispada, infinitos adjetivos pueden escribirse aquí… esa clase de persona que debe estar en la vida de uno y que se acaba haciendo indispensable, una altruista consumada que siempre se ha interesado por mi sin buscar nada a cambio, es glucosa pura.

A mi amigo desde tiempos inmemoriales, José (también conocido como Duque de Ager, Jox, Arkantos, Shurprimo y otros tantos seudónimos estúpidos que nos gustan tanto), parece increíble como alguien puede ser en ocasiones tan pesado y desquiciante (¿unas arenitas?, ¿un age?, el tren, el viento, etc) y al mismo tiempo puede sacarte una carcajada. A todo mi grupillo de los conocidos como “mis catalanes” y los CPS, siglas cuyo significado omitiré aquí pero que ellos conocen bien. Especialmente a Sergio por su generosidad, por pensar siempre en todos y por hacer grupo.

Siento el tocho que acabo de soltar, pero al final el *Orgullo y Prejuicio* ha dado más de si de lo que parecía, para acabar dándome cuenta de que es más importante centrarse en la calidad frente a la cantidad de personas a mi alrededor. Muchas gracias a todos.

D. Benito Alcaide Alañón, Catedrático de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid y **D. Pedro Almendros Requena**, Profesor de Investigación del Instituto de Química Orgánica General del Consejo Superior de Investigaciones Científicas.

CERTIFICAN:

Que la presente Memoria, titulada **ESTUDIO DE LA REACTIVIDAD DE SISTEMAS INSATURADOS FRENTE A ZWITTERIONES TIPO KOSHAR. APLICACIONES SINTÉTICAS**, ha sido realizada bajo su dirección en el grupo de **Lactamas y Heterociclos Bioactivos** (Unidad Asociada al CSIC) del Departamento de Química Orgánica I de la Universidad Complutense de Madrid, por el Licenciado en Química D. **Carlos Lázaro Milla**, y autorizan su presentación para ser calificada como Tesis Doctoral.

Madrid, 5 de julio de 2019

Fdo. Prof. Benito Alcaide, Prof. Pedro Almendros

Los resultados obtenidos e incluidos en esta Memoria se encuadran dentro del Plan de Investigación presentado para la consecución del Doctorado en Química Orgánica. Estos resultados han dado lugar a las siguientes publicaciones:

1. B. Alcaide, P. Almendros, C. Lázaro-Milla
   "Unveiling the Uncatalyzed Reaction of Alkynes with 1,2-Dipoles for the Room Temperature Synthesis of Cyclobutenes"
   Chem. Comm. **2015**, *51*, 3395-3398.

2. B. Alcaide, P. Almendros, C. Lázaro-Milla
   "Metal-Free [3+2] Cycloaddition of Azides with $Tf_2C{=}CH_2$ for the Regioselective Preparation of Elusive 4-(trifluoromethylsulfonyl)-1,2,3-triazoles"
   Chem. Commun. **2015**, *51*, 6992-6995.

3. B. Alcaide, P. Almendros, C. Lázaro-Milla
   "Direct Metal-Free Entry to Aminocyclobutenes or Aminocyclobutenols from Ynamides. Synthetic Applications"
   Chem. Eur. J. **2016**, *22*, 8998-9005.

4. B. Alcaide, P. Almendros, C. Lázaro-Milla
   "Regioselective Synthesis of Heteroatom-Functionalized Cyclobutene-triflones and Cyclobutenones"
   Adv. Synth. Catal. **2017**, *359*, 2630-2639.

5. P. Almendros, H. Yanai, S. Hoshikawa, C. Aragoncillo, C. Lázaro-Milla, M. Toledano-Pinedo, T. Matsumoto, B. Alcaide
   "Transition Metal-Free Controlled Synthesis of Bis[(trifluoromethyl)sulfonyl] ethyldecorated Heterocycles"
   Org. Chem. Front. **2018***, 5,* 3163-3169.

6. B. Alcaide, P. Almendros, C. Lázaro-Milla, P. Delgado-Martínez
   "Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization *versus* Rare Bis(cyclization)"
   Chem. Eur. J. **2018***, 24,* 8186-8194.

7. H. Yanai, P. Almendros, S. Takahashi, C. Lázaro-Milla, B. Alcaide, T. Matsumoto
   "Synthesis and Characterization of Stable Phosphorus Carbabetaines"
   Chem. Asian J. **2018***, 13,* 1956-1961.

8. B. Alcaide, P. Almendros, C. Lázaro-Milla
   "Convenient Access to 2,3-Disubstituted-cyclobut-2-en-1-ones under Suzuki Conditions and Their Synthetic Utility"
   Chem. Eur. J. **2019**, *25*, 7547-7552.

Los resultados obtenidos y no incluidos en esta Memoria por quedar fuera del Plan de Investigación han dado lugar a las siguientes publicaciones:

9. B. Alcaide, P. Almendros, E. Busto, C. Lázaro-Milla
   "Photoinduced Gold-Catalyzed Domino C(sp) Arylation/Oxyarylation of TMS-Terminated Alkynols with Arenediazonium Salts"
   J. Org. Chem. **2017**, *82*, 2177-2186.

10. B. Alcaide, P. Almendros, E. Busto, F. Herrera, C. Lázaro-Milla, A. Luna
"Photopromoted Entry to Benzothiophenes, Benzoselenophenes, 3*H*-Indoles, Isocoumarins, Benzosultams, and (Thio)flavones by Gold-Catalyzed Arylative Heterocyclization of Alkynes"
Adv. Synth. Catal. **2017**, *359*, 2640-2652.

11. B. Alcaide, P. Almendros, B. Aparicio, C. Lázaro-Milla, A. Luna, O. Nieto Faza
"Gold-Photoredox-Cocatalyzed Tandem Oxycyclization/Coupling Sequence of Allenols and Diazonium Salts with Visible Light Mediation"
Adv. Synth. Catal. **2017**, *359*, 2789-2800.

Abreviaturas utilizadas en esta Memoria

En la presente Tesis Doctoral se han utilizado las abreviaturas y acrónimos recomendados en *"Guidelines for Authors" (J. Org. Chem*. Versión actualizada 15 de diciembre de 2018) y las indicadas a continuación:

AAC	*alkyne-azide cycloaddition* (cicloadición alquino-azida)
AMCPB	ácido *m*-cloroperbenzoico
BCP	*bond critical points* (puntos de enlace críticos)
BHT	2,6-di-terc-butil-4-hidroxitolueno
BINAP	*2,2'-bis(diphenylphosphino)-1,1'-binaphthyl* (2,2′-bis(difenilfosfino)-1,1′-binaftilo)
BQ	benzoquinona
ca.	*circa* (aproximadamente)
CCF	cromatografía en capa fina
CFL	*compact fluorescent lamp* (lámpara fluorescente compacta)
col.	colaboradores
COX	ciclooxigenasa
CT	*charge transfer* (transferencia de carga)
CuAAC	*Copper-Catalyzed Azide-Alkyne Cycloaddition* (cicloadición alquino-azida catalizada por cobre)
DBU	1,8-diazabiciclo(5.4.0)undec-7-eno
DCE	dicloroetano
DCM	diclorometano
DFT	*density functional theory* (teoría del funcional de la densidad)
DMF	dimetilformamida
DMSO	dimetilsulfóxido
DMAD	acetilendicarboxilato de dimetilo
d.r.	*diastereomeric ratio* (relación diastereomérica)
e.g.	*exempli gratia* (por ejemplo)
equiv.	Equivalente

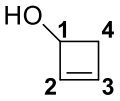
et al.	*et alii (*y otros)
DPPA	*diphenylphosphorilazide* (difenilfosforilazida)
EDG	*electron donating group* (grupo dador de electrones)
EWG	*electron withdrawing group* (grupo aceptor de electrones)
Het	heterociclo
HetA	heteroátomo o grupo funcional heteroatómico
IC50	*half maximal inhibitory concentration* (concentración inhibitoria para obtener un 50% del efecto máximo)
INT	intermedio
i.e.	*id est* (es decir)
MCPBA	*metacloroperbenzoic acid* (ácido *m*-cloroperbenzoico)
MW	*microwave* (microondas)
NBO	*natural bond orbital* (orbitales naturales de enlace)
NLMO	*natural localized molecular orbital* (localización natural de orbitales moleculares)
NPA	*natural population analysis* (modelo de análisis poblacional natural)
PCM	*polarizable continuum model* (modelo del continuo polarizable)
PFNB	*p*-fluoronitrobenceno
PMP	*p*-metoxifenilo
PS	*proton sponge* (esponja de protones)
QTAIM	*quantum theory atom in molecules* (teoría cuántica de átomos en moléculas)
Ref.	referencia
r.d.	relación de diastereómeros
RMN	resonancia magnética nuclear
RT	*room temperatura* (temperatura ambiente)
Rto.	rendimiento
RuAAC	*ruthenium-catalyzed azide-alkyne cycloaddition* (cicloadición alquino-azida catalizada por rutenio)

SEM-EDX	*scanning electron microscopy - energy dispersive X-ray spectroscopy* (microscopia electrónica de barrido con detector de energía de dispersión de rayos X)
SPAAC	*Strain-Promoted Alkyne-Azide Cycloadditions* (cicloadición alquino-azida promovida por tensión anular)
TBAF	*tetra-n-butylammonium fluoride* (fluoruro de tetrabutilamonio)
TBAI	*tetra-n-butylammonium iodide* (yoduro de tetrabutil amonio)
THF	tetrahidrofurano
T	temperatura
t	tiempo
Tf	trifluorometanosulfonilo
TIPS	triisopropilsilano
TLC	*thin layer chromatography* (cromatografía en capa fina)
TMS	trimetilsilano
TS	*transition state* (estado de transición)

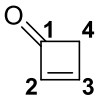
Nomenclatura y numeración utilizada en esta Memoria

La numeración y nomenclatura utilizada en esta Memoria para los compuestos sintetizados en la presente Tesis Doctoral es la que se indica a continuación:

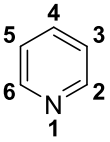
ciclobuteno



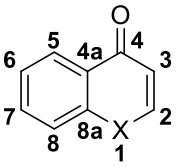
ciclobutenol
(ciclobut-2-en-1-ol)



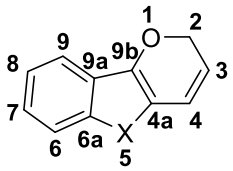
ciclobutenona
(ciclobut-2-en-1-ona)



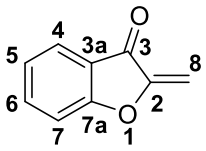
piridina



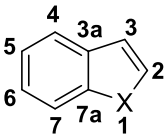
flavona
X = O, S, Se



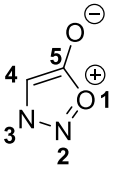
2*H*-pirano fusionado
X = O, S, NG



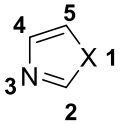
aurona



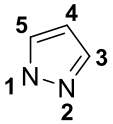
indol, X = N
benzofurano, X = O



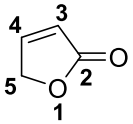
sidnona



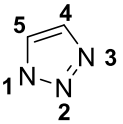
oxazol, X = O
tiazol, X = S
imidazol, X = N



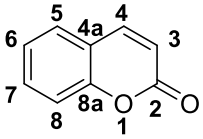
pirazol



furan-2(5*H*)-ona



1,2,3-triazol



cumarina

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I. INTRODUCCIÓN

I. INTRODUCCIÓN

Descubiertos en 1976, los zwitteriones de Koshar, no pasaron de ser más que una mera curiosidad científica. De hecho, Koshar y col. describieron su método de síntesis, pero no analizaron en detalle su estructura y mucho menos sus propiedades o reactividad, quedando en el olvido desde su publicación. No fue hasta 2013 cuando el grupo de Hikaru Yanai los rescató del olvido. Yanai y col. desarrollaron un método de síntesis más fácil y eficiente, llevando a cabo una minuciosa determinación estructural y estudiando sus particulares propiedades orbitalarias. También, consiguieron utilizar estos zwitteriones para producir alquilaciones, pero de alcance muy limitado, ya que solo era aplicable a anillos aromáticos fenólicos.

Basándonos en el estudio de Yanai y las propiedades que presentaban los zwitteriones en disolución, pensamos que sus aplicaciones no podían quedar restringidas a dichas alquilaciones. Vaticinamos entonces que estas particulares moléculas deberían ser capaces de reaccionar con otros tipos de sistemas aromáticos, así como con diferentes sistemas insaturados. La investigación de estas premisas ha sido el objetivo central de la presente Tesis.

Por otro lado, las estructuras cíclicas tensionadas siempre han demostrado ser de gran interés en Química Orgánica. Su inherente tensión de anillo les confiere unas propiedades y reactividad particulares que las hace tremendamente útiles en Síntesis Orgánica. En especial, los ciclobutenos, que además poseen un doble enlace en su estructura, son materiales de partida muy útiles. Adicionalmente, las ciclobutenonas, poseen un grupo carbonilo, lo que incrementa su versatilidad. Sin embargo, como aspecto negativo de estos compuestos hay que mencionar que suelen ser difíciles de obtener, mucho más si se desean conseguir regio-, quimio- o estereoselectivamente.

Los ciclobutenoles también forman parte de la familia de anillos tensionados y comparte con ellos las mismas ventajas e inconvenientes, pero además sus métodos de síntesis están aún más restringidos pues la mayoría se obtienen por reducción de ciclobutenonas.

Por otra parte, las flavonas son un tipo de heterociclo dentro del grupo de los flavonoides, los cuales presentan un interés creciente debido a sus actividades biológicas *in vitro* e *in vivo*. Por ello, el desarrollo de nuevas estrategias sintéticas

que permitan introducir nuevos sustituyentes en su núcleo resulta de gran importancia.

Otros heterociclos de gran relevancia son los triazoles, en especial los 1,2,3-triazoles. Estos han demostrado tener una gran variedad de aplicaciones en el campo de la farmacología, en química biológica, química supramolecular, química de materiales y por supuesto en Síntesis Orgánica, constituyendo un sintón muy versátil para la construcción de estructuras más complejas. Por todo ello, se invierte un gran esfuerzo en el desarrollo de nuevas metodologías para obtener este heterociclo.

Compuestos completamente diferentes a los anteriores son las betaínas de fósforo. Son un importante grupo de compuestos dada su estructura, propiedades y reactividad. Su simple presencia como intermedios en la reacción de Wittig (1,4-oxabetaínas) nos sirve para hacernos una idea de su impacto. En este contexto, la síntesis y estudio de 1,3- y 1,4-carbabetaínas resulta de gran interés para conocer su estructura y propiedades.

Por otro lado, la funcionalización selectiva de heterociclos en posiciones C−H resulta un gran reto. La ausencia de un grupo funcional que dirija y controle la quimioselectividad del proceso provoca en la mayoría de casos la obtención de mezclas de productos. La alquilación de estas posiciones de manera totalmente selectiva, sin catalizador y en condiciones suaves constituye un *rara avis* en este campo de la Química Orgánica. Estas alquilaciones son importantes, pues permiten introducir modificaciones estructurales en los compuestos para mejorar algún aspecto de sus propiedades sin afectar a otras. Especialmente, en farmacología, estos procesos de derivatización son ampliamente utilizados, pues permiten modificar principios activos ya existentes para mejorar su actividad o encontrar nuevas aplicaciones con un coste económico reducido.

Por último, si a todas las estructuras mencionadas en esta introducción añadimos la posibilidad de incorporar simultáneamente flúor en su estructura, aumentaremos el interés de las metodologías sintéticas desarrolladas en la presente Tesis, ya que las moléculas orgánicas fluoradas exhiben actividades biológicas peculiares debido a su mayor lipofilia y estabilidad metabólica. En este contexto, el grupo trifluorometanosulfonilo es particularmente relevante debido a su efectividad

para la modificación de las propiedades químicas de los compuestos orgánicos sin cambiar la complejidad molecular.

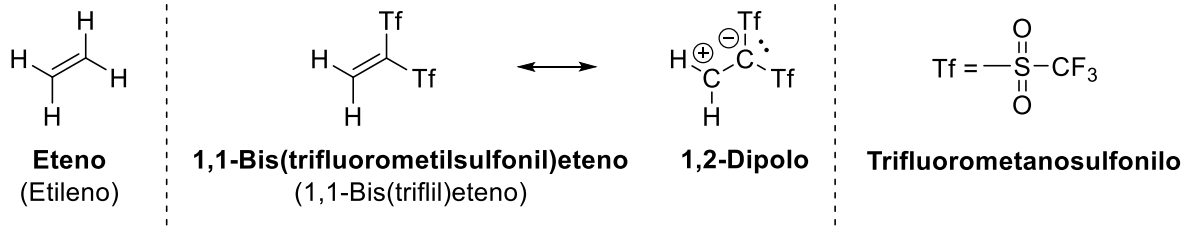
II. ANTECEDENTES GENERALES

II. ANTECEDENTES GENERALES

II.1. Zwitteriones de Koshar

La generación de moléculas altamente polarizadas ha resultado siempre de gran interés en Química Orgánica. El estudio de sus estructuras poco comunes suscita curiosidad, debido a que las localizaciones de carga parciales provocan distorsiones orbitalarias. Adicionalmente, su utilidad sintética ha sido ampliamente investigada.[1]

De entre toda esta familia de moléculas, nuestro grupo de trabajo decidió centrarse en el estudio de la molécula de 1,1-bis(trifluorometilsulfonil)eteno (Esquema II.1).



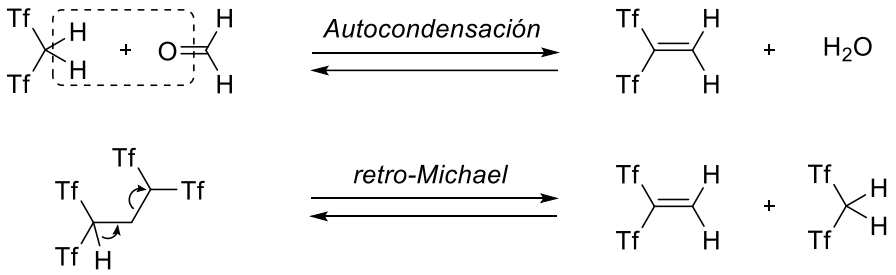
Esquema II.1

Esta olefina puede definirse como una molécula de etileno en la que uno de sus átomos de carbono ha sido funcionalizado con dos grupos trifluorometanosulfonilo (Tf). Este grupo funcional es uno de los más electroatractores en Química Orgánica. Por tanto, la presencia de dos grupos Tf sobre un mismo carbono provoca una distorsión en la nube π de electrones de la olefina, es decir, se produce una polarización del doble enlace, observándose una fuerte diferencia de densidad electrónica en su superficie. De hecho, esta molécula está tan altamente polarizada que debe ser considerada un híbrido de dos formas resonantes, entre la olefina y su forma de 1,2-dipolo. Esta última forma resonante va a ser la responsable de la reactividad que presenta este compuesto.

[1] a) *Cycloaddition Reactions in Organic Synthesis*, S. Kobayashi, K. A. Jørgensen, Wiley-VCH, Weinheim, Alemania, **2002**; b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, ed. A. Padwa, W. H. Pearson, John Wiley & Sons, Chichester, Reino Unido, **2003**.

El problema principal que comparte esta molécula con otros dipolos es su obtención y almacenamiento. Al tratarse de moléculas muy reactivas no pueden ser sintetizadas y almacenadas para su posterior uso, pues la inestabilidad intrínseca que poseen provoca su descomposición en periodos cortos de tiempo. Se hace necesario, por tanto, su formación *in situ* para llevar a cabo inmediatamente las reacciones en las que vayan a estar implicados.

En la bibliografía encontramos dos métodos principales para generar la molécula de $Tf_2C{=}CH_2$, que consisten por un lado en una autocondensación[2] de bis(triflil)metano (Tf_2CH_2) con formaldehido ($H_2C{=}O$) y por otro en una reacción retro-Michael[3] de $Tf_2CHCH_2CHTf_2$ (Esquema II.2).



Esquema II.2

El primer método ha sido utilizado en la síntesis de ariltriflonas[2b] a partir de ciclohexenos obtenidos por cicloadición Diels-Alder entre 1,3-dienos y la molécula de $Tf_2C{=}CH_2$. El método retro-Michael se ha aplicado satisfactoriamente[4] para hacer reaccionar la molécula de $Tf_2C{=}CH_2$ con nucleófilos neutros, arenos ricos en electrones y compuestos 1,3-dicarbonílicos.[5] Sin embargo, el uso de estos métodos se encuentra bastante limitado por la presencia en el medio de reacción de los compuestos Tf_2CH_2 y $Tf_2CHCH_2CHTf_2$ los cuales poseen una acidez elevada que

---

2 a) R. J. Koshar, L. L. Barber, Jr., US Patent 4 053 519, **1977;** b) H. Yanai, M. Fujita, T. Taguchi, *Chem. Commun*. **2011**, *47*, 7245. El termino autocondensación (traducido del inglés "self-condensation") es utilizado por estos autores para referirse a esta reacción en particular. En todo caso, no hace referencia a los procesos clásicos de autocondensación de aldehídos y cetonas.

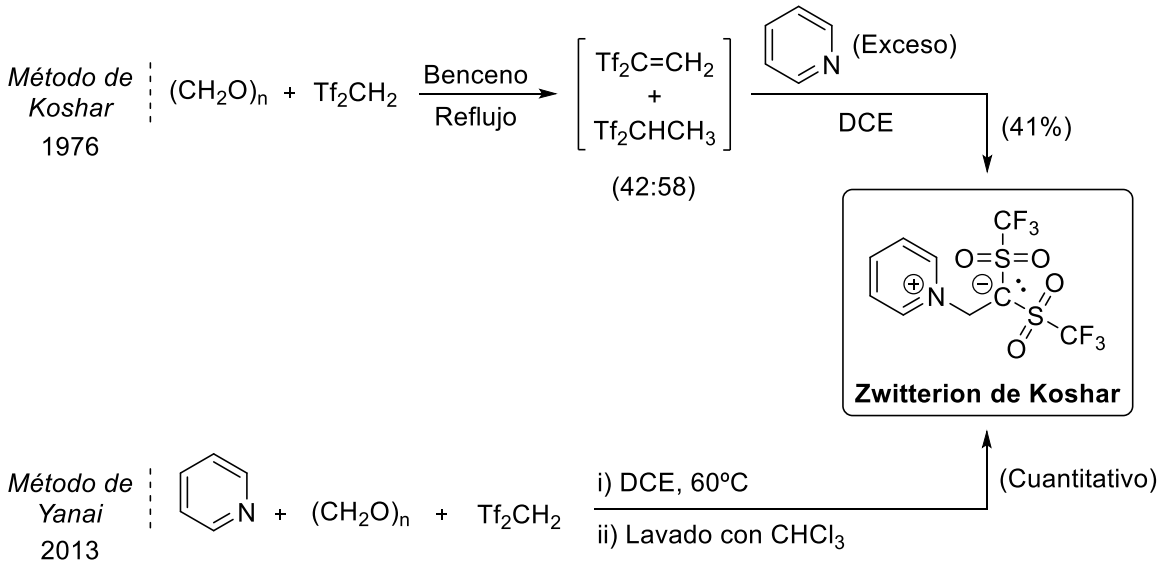
3 H. Yanai, T. Yoshino, M. Fujita, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Angew. Chem. Int. Ed.* **2013**, *52*, 1560.

4 a) H. Yanai, H. Ogura, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Chem. Eur. J.* **2011**, *17*, 11747; b) H. Yanai, M. Fujita, A. Takahashi, M. Zhang, M. Mishima, A. Kotani, T. Matsumoto, T. Taguchi, *Molecules* **2013**, *18*, 15531.

5 Para una visión global de los métodos de generación *in situ* de $Tf_2C{=}CH_2$ y sus aplicaciones sintéticas consultar: H. Yanai, *Chem. Pharm. Bull.* **2015**, *63*, 649.

degrada muchos grupos funcionales sensibles (pK_a = 2.1 para Tf_2CH_2 en DMSO). De ahí el interés en encontrar un método para generar *in situ* la molécula altamente polarizada $Tf_2C{=}CH_2$ sin estos inconvenientes.

En 1976, Koshar y col. describieron que la reacción de Tf_2CH_2 con paraformaldehido $(CH_2O)_n$ originaba una mezcla 42:58 de $Tf_2C{=}CH_2$ y Tf_2CHCH_3. Si dicha mezcla se trataba con piridina se obtenía una sal de piridinio estable que más tarde fue conocida como zwitterión de Koshar.[6] Este tipo de zwitteriones contienen un carbanión estabilizado por la bis-sustitución con dos grupos triflilo (trifluorometanosulfonilo) (Esquema II.3).



Esquema II.3

Koshar publicó sus resultados, pero no estudió las propiedades estructurales del zwitterión y mucho menos sus posibles aplicaciones sintéticas, permaneciendo durante años en el olvido como una mera curiosidad científica.

Afortunadamente, Yanai y col. volvieron a interesarse por esta peculiar estructura.[7] Primero, desarrollaron un método de síntesis que mejoraba el propuesto por Koshar a través de una reacción multicomponente de piridina, paraformaldehido y bis(triflil)metano, utilizando dicloetano como disolvente a 60ºC y en un solo paso de reacción. El posterior lavado con cloroformo del sólido formado,

6 L. L. Barber Jr, R. J. Koshar, US Pat., 3 962 342, **1976**.

7 a) H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi, T. Matsumoto, *Chem. Commun.* **2013**, *49*, 10091; b) H. Yanai, R. Takahashi, Y. Takahashi, A. Kotani, H. Hakamata, T. Matsumoto, *Chem. Eur. J.* **2017**, *23*, 8203.

permitió obtener el zwitterión de Koshar con una pureza y rendimientos excelentes (Esquema II.3). Este grupo japonés utilizó su método de síntesis para obtener otras muchas sales equivalentes con piridinas diferentemente sustituidas y otros heterociclos nitrogenados (Figura II.1). Nuestro grupo de trabajo también desarrolló nuevos zwitteriones tipo Koshar como se verá en los siguientes Capítulos.

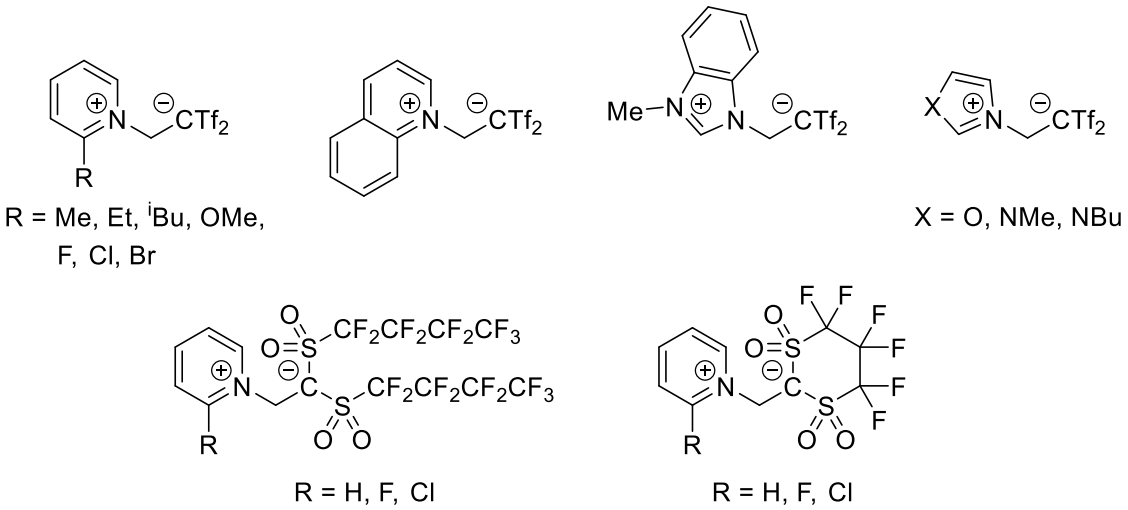


Figura II.1

Además de mejorar el proceso sintético, Yanai estudió profundamente su estructura y propiedades orbitalarias lo que permitió explicar cómo es posible que estas moléculas sean sólidos no higroscópicos tan estables a la luz, a la atmósfera e incluso a altas temperaturas.

De entre las propiedades estudiadas por Yanai la más importante es la que explica la estabilidad del carbanión $[Tf_2C]^-$ dentro del zwitterión. Aparte del fuerte efecto inductivo y los efectos conjugativos producidos por los dos grupos Tf, lo que les permite deslocalizar la carga, existe un efecto estabilizante adicional denominado hiperconjugación negativa. Este efecto es consecuencia del solapamiento parcial de los orbitales moleculares antienlazantes de los enlaces contiguos al carbono aniónico C^-. Es decir, se producen solapamientos entre el orbital *p* de C^-, en el cual se encuentra el par de electrones libre, el orbital molecular antienlazante $\sigma^*_{C(H)_2-N}$ y dos orbitales molecular antienlazantes $\sigma^*_{S-C(F)_3}$ (uno por cada enlace $S-C(F)_3$). Ello explica el acortamiento de las distancias de enlace entre C^- y CH_2 y la elongación simultánea del enlace $C(H)_2-N$ y el mismo efecto de acortamiento en el enlace C^--S y elongación $S-C(F)_3$. Estos resultados indican que la hiperconjugación negativa

permite la deslocalización del par de electrones libre en los tres orbitales σ^* adyacentes, jugando un papel fundamental en la estabilidad de la molécula (Figura II.2).

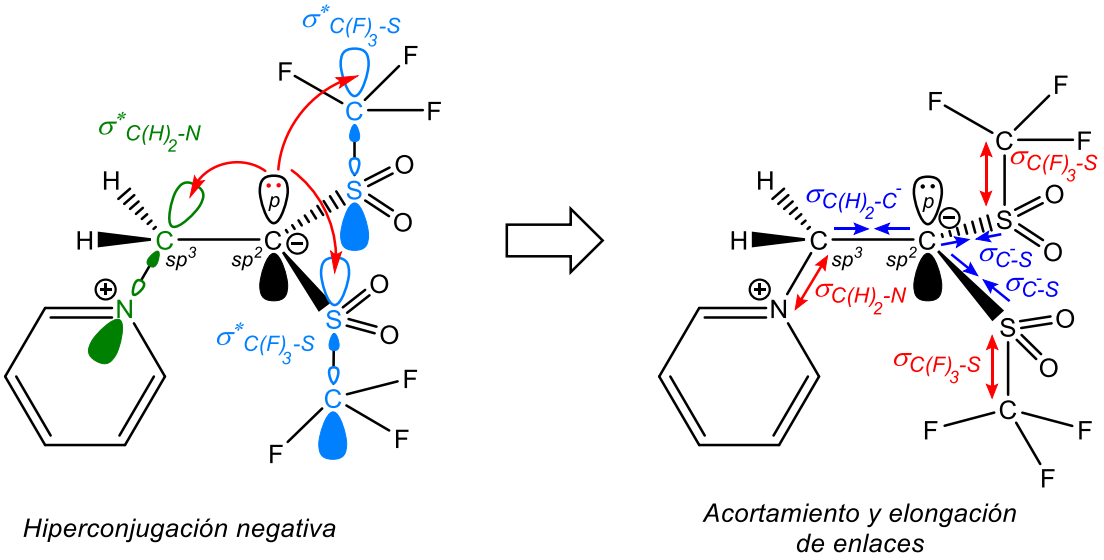
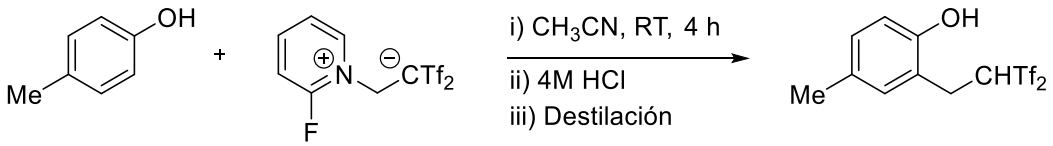


Figura II.2

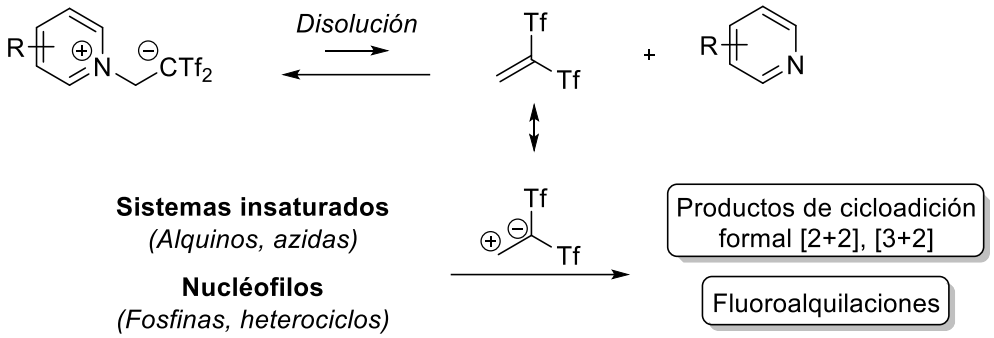
Los diferentes factores que contribuyen a la deslocalización de la carga negativa hacen que el carbanión $[Tf_2C]^-$ se encuentre muy estabilizado. Esta gran estabilización es responsable de su alta acidez y su baja nucleofilia.

Además, Yanai describió la primera reacción de un zwitterión tipo Koshar, consistente en la C-alquilación de un fenol con la incorporación del grupo CH_2CHTf_2 (Esquema II.4).



Esquema II.4

Esta reacción demostró que es posible utilizar los zwitteriones de Koshar como fuente latente de $Tf_2C{=}CH_2$, generándose *in situ* por el equilibrio que se establece cuando el zwitterión se encuentra en disolución (Esquema II.5).

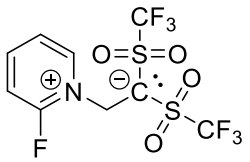


Esquema II.5

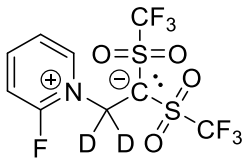
De este modo, los zwitteriones de Koshar se convierten en la alternativa perfecta a los métodos de autocondensación y retro-Michael, pues permiten generar $Tf_2C{=}CH_2$ sin los inconvenientes de estos, dado que no se genera ningún subproducto de acidez o basicidad elevada.

Gracias a las propiedades inusuales de estos compuestos, nos planteamos encontrar cual era el zwitterión con mejor comportamiento en disolución para poder estudiar la reactividad de la molécula de $Tf_2C{=}CH_2$ frente a diferentes sistemas insaturados y diversos nucleófilos no explorados previamente, lo cual ha sido el fundamento de esta Tesis Doctoral.

Como se verá en los diferentes Capítulos y en la Discusión General, determinaremos que el zwitterión que mejores resultados aporta para desarrollar la reactividad de la mólecula $Tf_2C{=}CH_2$ es el derivado de la 2-fluoropiridina, conocido como reactivo de Yanai, dado que fue este investigador el primero en describirlo. Nuestro grupo de investigación ha desarrollado su versión deuterada (Figura II.3).



Reactivo de Yanai



[D_2]-*Reactivo de Yanai*

Figura II.3

II.2. Ciclobutenos

II.2.1. Síntesis y aplicaciones

Los ciclobutenos son compuestos cíclicos de carbono, constituidos por cuatro eslabones con un doble enlace carbono-carbono en su estructura (Figura II.4).

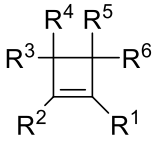
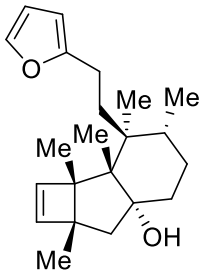
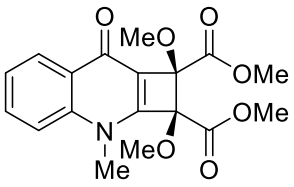


Figura II.4

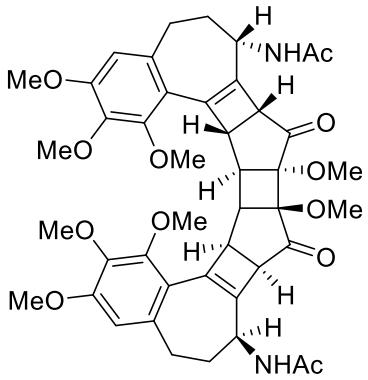
Esta configuración anular tensionada, acentuada por el doble enlace, les confiere unas propiedades químicas particulares, pero también dificulta su obtención. Son compuestos atractivos, presentes en productos naturales y compuestos biológicamente activos.[8] Algunos ejemplos de productos naturales que incluyen un anillo de ciclobuteno en su estructuraestán recogidos en la Figura II.5.



Illudano



Cyclomegistina



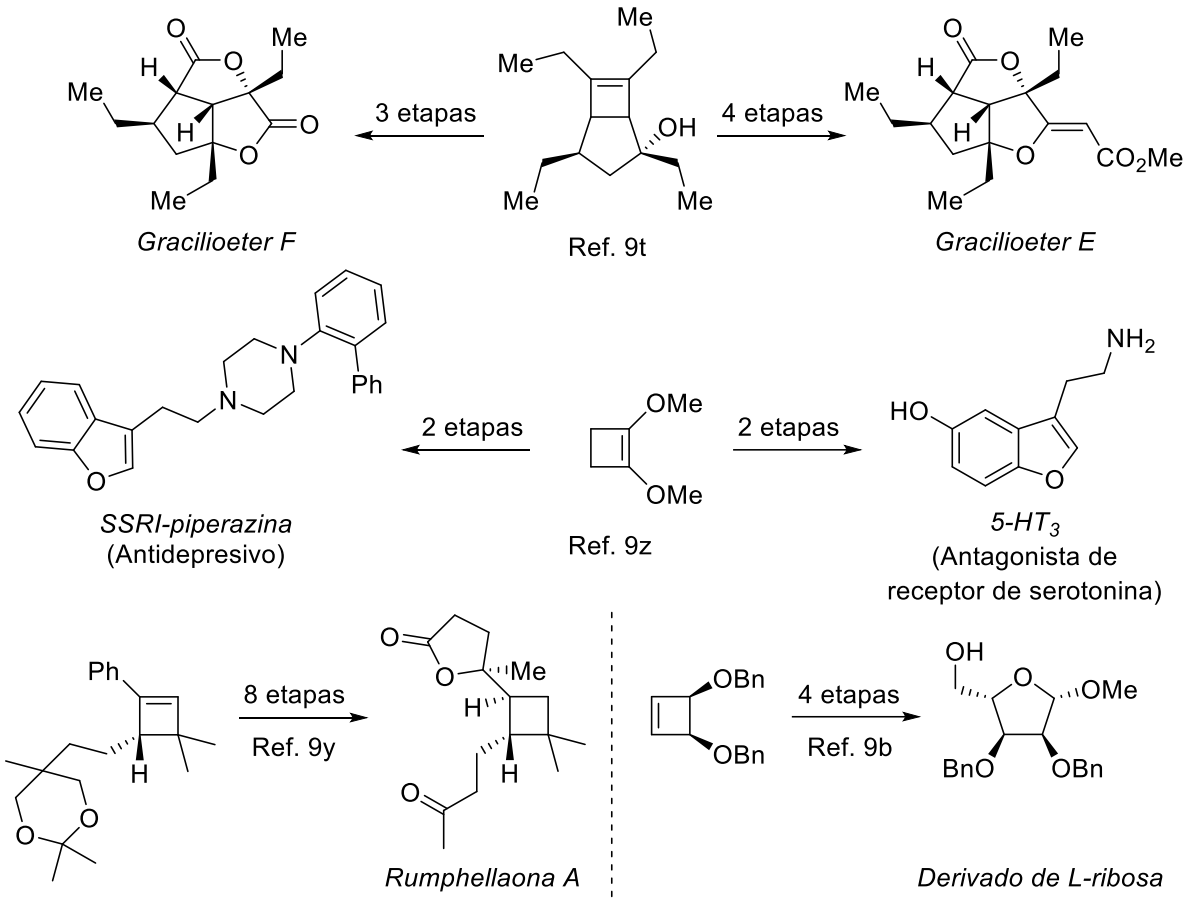
α-Lumicolchicina

Figura II.5

También son precursores útiles para la construcción de estructuras más complejas.[9] Algunos ejemplos seleccionados se muestran en el Esquema II.6.

[8] a) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449; b) J.-J. Tan, C.-H. Tan, Y.-Q. Wang, S.-H. Jiang, D.-Y. Zhu, *Helv. Chim. Acta* **2006**, *89*, 117; c) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052; d) V. M. Dembitsky, J. Nat. Med. **2008**, *62*, 1; e) Y. Aoyagi, A. Yamazaki, R. Kato, F. Tobe, H. Fukaya, T. Nishikawa, A. Nakahashi, N. Miura, K. Monde, K. Takeya, *Tetrahedron Lett*. **2011**, *52*, 1851; f) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed*. **2011**, *50*, 7740.

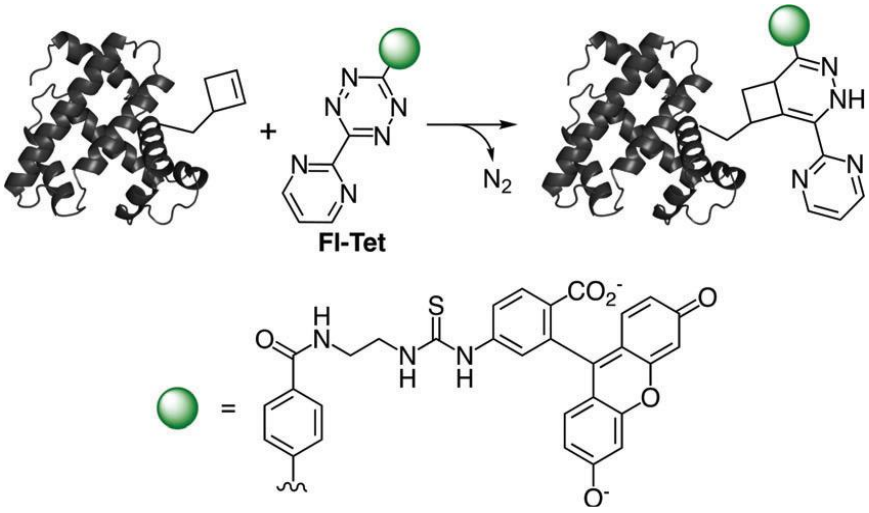
[9] Para publicaciones recientes véanse: a) X.-N. Wang, E. H. Krenske, R. C. Johnston, K. N. Houk, R. P. Hsung, *J. Am. Chem. Soc.* **2014**, *136*, 9802; b) R. H. Grubbs, J. Hartung, *Angew. Chem. Int. Ed.*



Esquema II.6

2014, *53*, 3885; c) M. Eisold, D. Didier*, Angew. Chem. Int. Ed.* **2015**, *54*, 15884; d) S. Yang, W. Yuan, Q. Xu, M. Shi, *Chem. Eur. J.* **2015**, *21*, 15964; e) M. J. Ralph, D. C. Harrowven, S. Gaulier, S. Ng, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2015**, *54*, 1527; f) N. Arichi, K. Yamada, Y. Yamaoka, K. Takasu, *J. Am. Chem. Soc.* **2015**, *137*, 9579; g) C. Souris, A. Misale, Y. Chen, M. Luparia, N. Maulide, *Org. Lett.* **2015**, *17*, 4486; h) B. D. Robertson, R. E. M. Brooner, R. A. Widenhoefer, *Chem. Eur. J.* **2015**, 21, 5714; i) X. Mao, P. Song, Y. Hao, Z. Sun, X. Hu, *Adv. Synth. Catal*. **2016**, *358*, 3719; j) P.-H. Chen, G. Dong, *Chem. Eur. J.* **2016**, 22, 18290; k) S. Reboredo, R. M. Girln, S. Filippone, T. Mikie, T. Sakurai, S. Seki, N. Martín, *Chem. Eur. J.* **2016**, *22*, 13627; l) W. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2016**, *138*, 10684; m) M. Guisán-Ceinos, A. Parra, V. Martín-Heras, M. Tortosa, *Angew. Chem. Int. Ed.* **2016**, *55*, 6969; n) M. Eisold, G. M. Kiefl, D. Didier, *Org. Lett.* **2016**, *18*, 3022; o) T. Matsuda, T. Matsumoto, *Org. Biomol. Chem.* **2016**, *14*, 5023; p) Y. Qiu, B. Yang, C. Zhu, J.-E. Bückvall, *Angew. Chem. Int. Ed.* **2016**, *55*, 6520; q) T. Kang, S. Ge, L. Lin, Y. Lu, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2016**, *55*, 5541; r) B. Ranieri, C. Obradors, M. Mato, A. M. Echavarren, *Org. Lett.* **2016**, *18*, 1614; s) P. Song, Q. Li, C. Wang, W. Wu, X. Mao, J. Wang, X. Hu, *Adv. Synth. Catal.* **2016**, *358*, 1208; t) S. A. Ruider, E. M. Carreira, *Org. Lett.* **2016**, *18*, 220; u) S. Blouin, V. Gandon, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2016**, *55*, 7208; v) M. Eisold, A. N. Baumann, G. M. Kiefl, S. T. Emmerling, D. Didier, *Chem. Eur. J.* **2017**, 23, 1634; w) T. Kurohara, M. Shibuya, Y. Yamamoto, *Adv. Synth. Catal.* **2017**, *359*, 1413; x) S. Blumberg, S. F. Martin, *Org. Lett.* **2017**, 19, 790; y) C. García-Morales, B. Ranieri, I. Escofet, L. López-Suarez, C. Obradors, A. I. Konovalov, A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 13628; z) S. Porcu, S. Demuro, A. Luridiana, A. Cocco, A. Frongia, D. J. Aitken, F. Charnay-Pouget, R. Guillot, G. Sarais, F. Secci, *Org. Lett.* **2018**, *20*, 7699; z') W. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2019**, *58*, 2500.

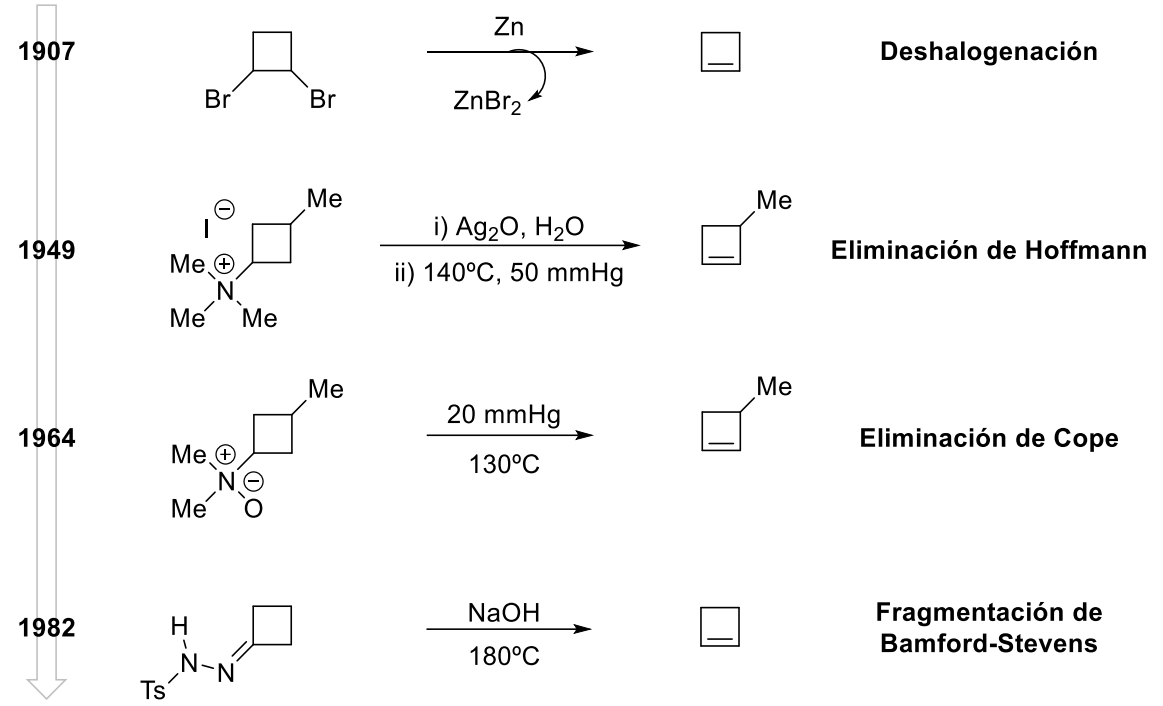
También se ha encontrado su utilidad en bioquímica formando parte de sondas, donde un ciclobuteno actúa como grupo reactivo en un aminoácido de una proteína modificada. A través de él, mediante una reacción Diels-Alder de demanda electrónica inversa con una tetrazina, es capaz de unir la proteína a un marcador químico fluorescente (Esquema II.6).[10]



Esquema II.6

A lo largo del siglo XX se desarrollaron diferentes métodos para obtener estos carbociclos insaturados. Una de las estrategias más utilizada se basó en la utilización de reacciones de eliminación, tales como las reacciones de deshalogenación, [11] eliminación de Hoffman, [12] eliminación de Cope, [13] y fragmentación de Bamford-Stevens[14] (Esquema II.7).

[10] K. Liu, B. Enns, B. Evans, N. Wang,a X. Shang, W. Sittiwong, P. H. Dussault, J. Guo, *Chem. Commun.* **2017**, *53*, 10604.
[11] R. Willstätter. J. Bruce, *Chemische Berichte* **1907**, *40*, 3979.
[12] J. D. Roberts, C. W. Sauer, *J. Am. Chem. Soc.* **1949**, 71, 3925.
[13] E. Gil-Av, J. Shabtai, *J. Org. Chem.* **1964**, *29*, 257.
[14] U. H. Brinker, G. Schenker, *J. Chem. Soc. Chem. Comm.* **1982**, 679.



Esquema II.7

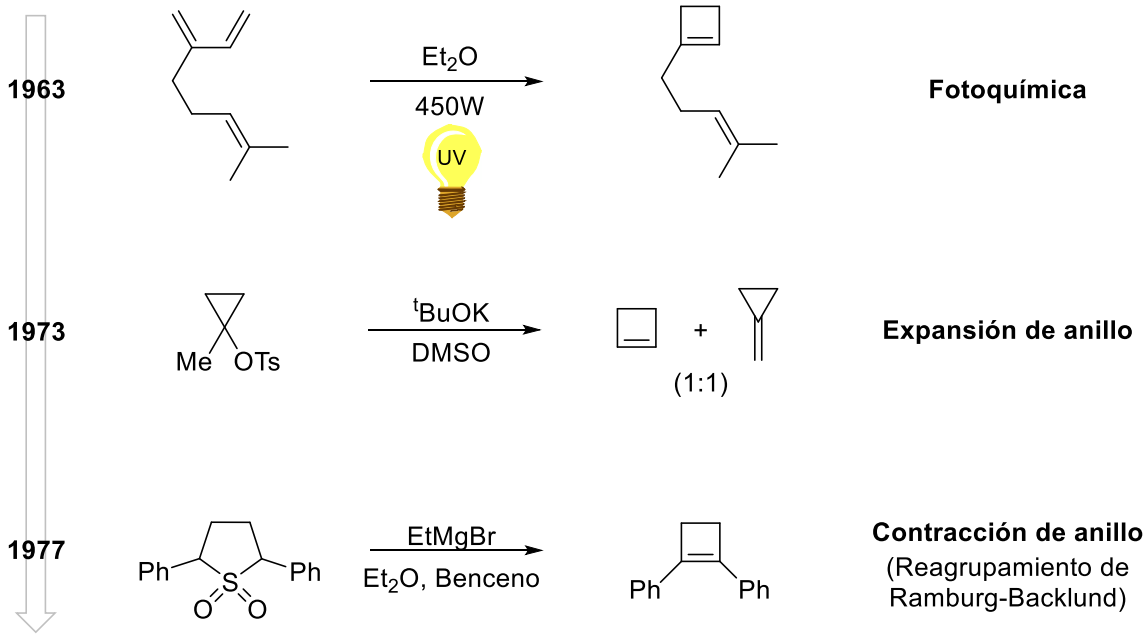
El método inicialmente utilizado en la primera década del siglo XX consistió en la eliminación (deshalogenación) del 1,2-dibromociclobutano con zinc metálico. Más adelante, la eliminación de Hoffmann, también permitió acceder a ciclobutenos por termólisis de un hidróxido de amonio cuaternario generado *in situ* por metilación de una amina terciaria y posterior intercambio iónico con óxido de plata. Esta eliminación se produce en condiciones de alta temperatura y baja presión. La eliminación de Cope, similar a la anterior, provoca la termólisis de un N-óxido en condiciones de vacío. Finalmente, dentro del grupo de reacciones más clásicas, la fragmentación de Bamford-Stevens involucra la fragmentación de una tosil-hidrazona en presencia de una base fuerte y altas temperaturas.

Desde mediados del siglo XX empiezan a aparecer otras estrategias para acceder al núcleo de ciclobuteno. Entre ellas encontramos procesos fotoquímicos[15] y aquellos que implican una expansion[16] o contracción[17] de anillo (Esquema II.8).

[15] a) R. Srinivasan, *J. Am. Chem. Soc.* **1963**, 85, 4045; b) K. J. Crowley, *Tetrahedron* **1965**, *21*, 1001; c) W. Adam, T. Oppenlaender, G. Zang, *J. Am. Chem. Soc.* **1985**, *107*, 3921.

[16] W. R. Dolbier, Jun, J. H. Alonso, *J. Chem. Soc. Chem. Comm.* **1973**, 394.

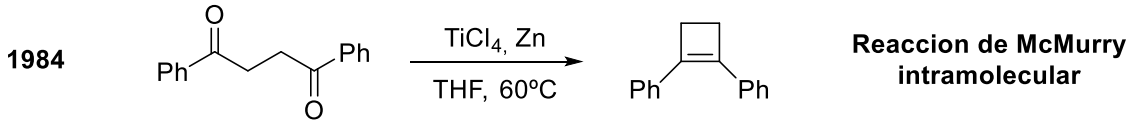
[17] a) L. A. Paquette, *Org. React*. **1977**, *25*, 1; b) R. M. Dodson, P. A. G. Zielske, *Chem. Commun.* **1965**, 353.



Esquema II.8

La fotociclación por cierre electrocíclico de 1,3-dienos mediante la aplicación prolongada de luz ultravioleta supuso una novedad importante en este campo. La reacción de expansión de anillo implica el tratamiento de un ciclopropil-metil-tosilato con *terc*-butóxido potásico, lo cual origina una mezcla 1:1 del ciclobuteno y metilenciclopropano. Por último, la reacción de reagrupamiento de Ramburg-Backlund implica una contracción de anillo por extrusión de SO_2 en una sulfona cíclica de cinco eslabones.

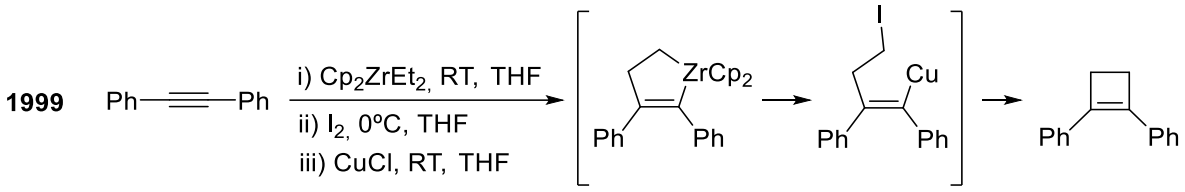
A medida que avanza el tiempo, en la década de los 80, empiezan a aparecer nuevos métodos sintéticos más selectivos y con condiciones más suaves pero asociados inexorablemente, a partir de este momento, a catalizadores metálicos. Uno de los primeros métodos en utilizar metales fue la reacción de McMurry intramolecular[18] (Esquema II.9).



Esquema II.9

[18] F. Toda, Y. Takehira, Y. Kataoka, K. Mori, T. Sato, M. Segawa, *J. Chem. Soc., Chem. Commun.* **1984**, *0*, 1234.

En los albores del siglo XXI, el uso de metales está totalmente integrado en este campo y se van desarrollando metodologías con catalizadores metálicos cada vez más sofisticados. Un ejemplo interesante es el publicado por el grupo de Takahashi y col. que utiliza un catalizador de circonio, $CuCl_2$ y I_2 para conseguir ciclobutenos a partir de alquinos[19] (Esquema II.10).



Esquema II.10

Los métodos mostrados hasta ahora son solo una muestra representativa de los más destacados a lo largo del tiempo en el siglo XX, pero existen otros muchos coetáneos a estos como por ejemplo la fragmentación de Shapiro, [20] la fragmentación de Chugaev[21] o la eliminación de Burgess,[22] entre otras.

La existencia de tantos métodos demuestra el interés que suscita este anillo tensionado en Química Orgánica y cómo no se ha parado de buscar nuevas metodologías para acceder a él. Sin embargo, estos protocolos tradicionales, aunque variados, se encuentran bastante limitados en algunos aspectos. Por ejemplo, presentan graves inconvenientes pues generalmente los rendimientos son bajos y suelen requerir de condiciones fotoquímicas o térmicas enérgicas, que pueden ser incompatibles con el control de la selectividad, así como con otros grupos funcionales sensibles presentes.

Por ello, en la actualidad, se hacen grandes esfuerzos en encontrar métodos que esquiven estos problemas. El desarrollo de las metodologías modernas busca combinar condiciones suaves con procesos en un solo paso de reacción. Para ello la estrategia más popular es la preparación de ciclobutenos por reacción de cicloadición [2+2] de alquinos con sistemas insaturados.[23] La cicloadición [2+2] de

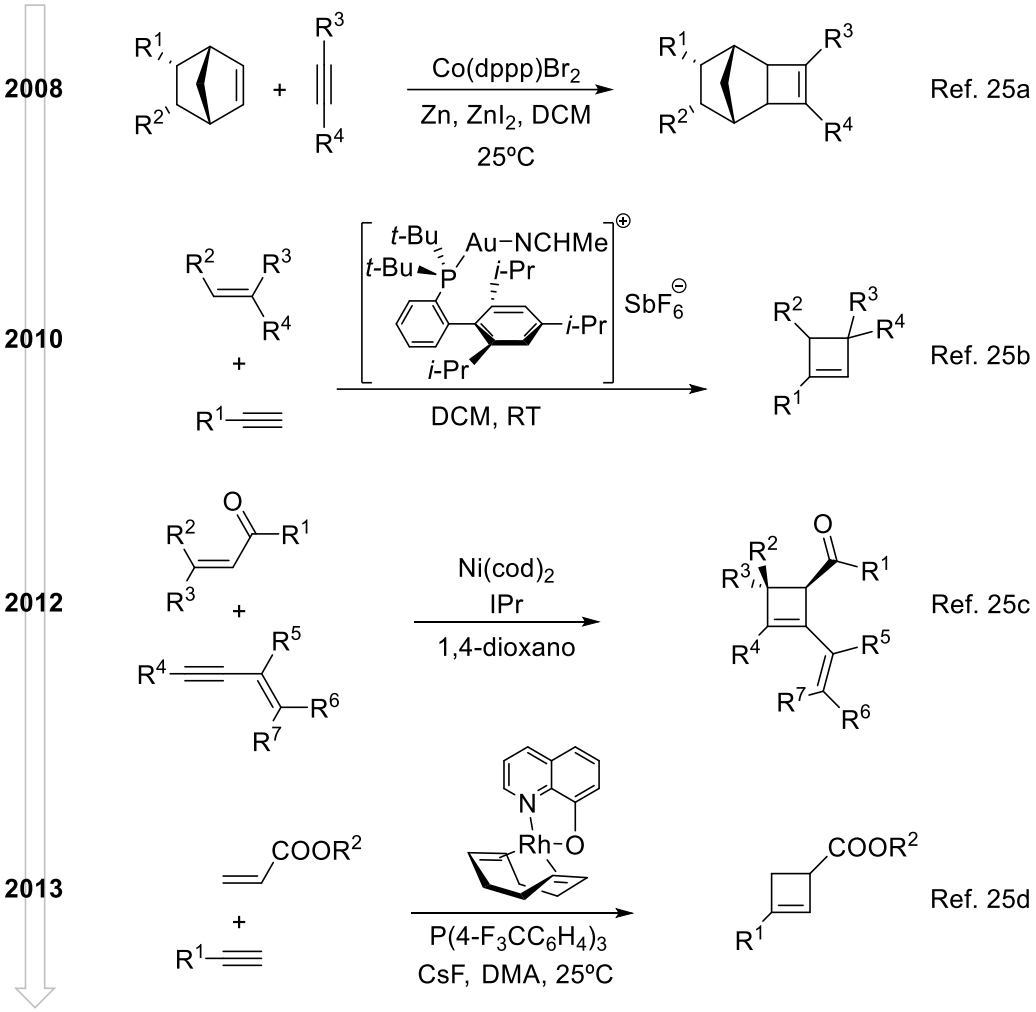
[19] T. Takahashi, B. Shen, K. Nakajima, Z. Xi, *J. Org. Chem.* **1999**, *64*, 8706.
[20] I. E. Dolgii, E. A. Shapiro, O. M. Nefedov, *Russ. Chem. Bull.* **1975**, *24*, 1569.
[21] L. Tschugaeff, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3118.
[22] E. Burgess, H. R. Penton, Jr. E. A. Taylor; *J. Org. Chem*. **1973**, *38*, 26.
[23] *Alkynes in cycloadditions*, ed. M. I. Alexandrovna, B. I. Ionin, J. C. Tebby, John Wiley & Sons Ltd, Chichester, Reino Unido, 2014.

alquinos con alquenos es la más común y se ha estudiado tanto en condiciones fotoquímicas o térmicas como por catálisis de metales de transición. Debe tenerse en cuenta que la transformación térmica [π2s + π2s] es un proceso prohibido según los principios de simetría orbital de Woodward-Hoffmann,[24] lo cual dificulta los procesos por esta vía. Aun así, encontramos en la bibliografía diferentes ejemplos de este tipo de cicloadición, pero en la mayoría de los casos se sugiere la aparición de intermedios radicalarios o iónicos para reacciones térmicas y fotociclaciones, por lo que es más correcto hablar de cicloadiciones formales [2+2].

Algunos ejemplos de procedimientos modernos basados en procesos [2+2] promovidos por catalizadores metálicos[25] se muestran en el Esquema II.11.

[24] R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

[25] a) J. Treutwein, G. Hilt, *Angew. Chem. Int. Ed.* **2008**, *47*, 6811; b) V. Lopez-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292; c) A. Nishimura, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2012**, *134*, 15692; d) K. Sakai, T. Kochi, F. Kakiuchi, *Org. Lett.* **2013,** *15,* 5.



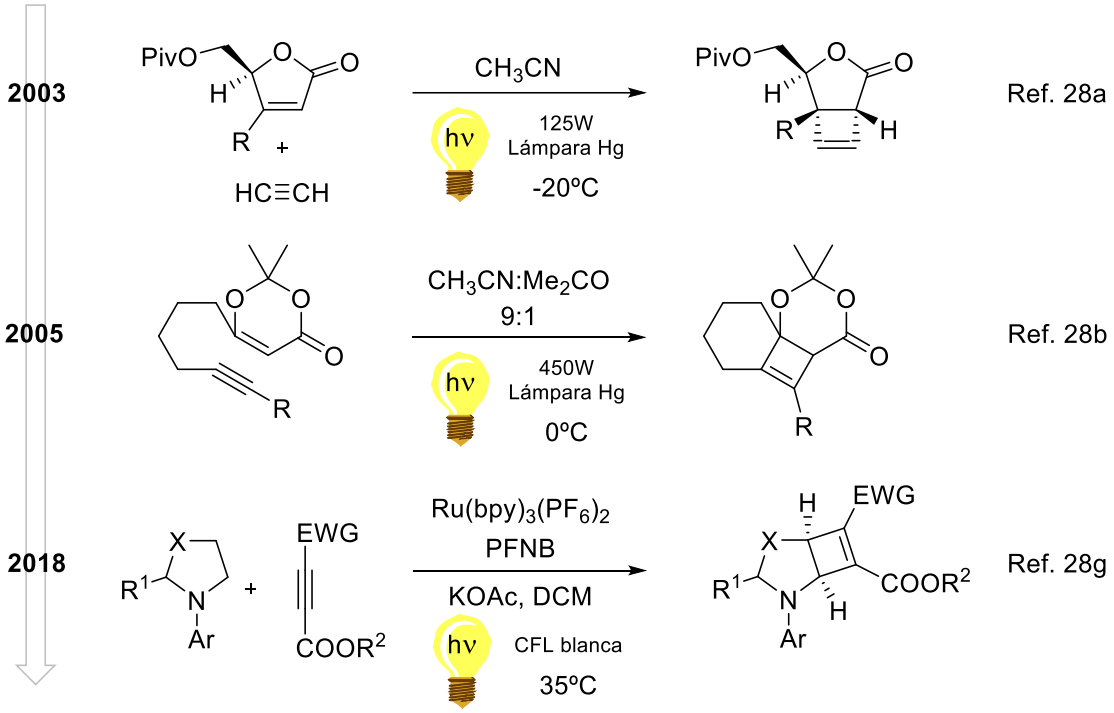
Esquema II.11

Aunque la tendencia actual en este campo es el uso de cada vez más tipos de catalizadores metálicos para acceder al anillo de ciclobuteno, no está exento de inconvenientes, debido a que estos métodos suelen estar restringidos a sustratos concretos y con una selectividad moderada.[25c,26] Además, el uso de catalizadores metálicos tiene el inconveniente de ser en la mayoría de casos costosos económicamente y poco respetuosos con el medio ambiente. [25b,27]

[26] a) N. Cockburn, J. Goodreid, W. Tam, *Curr. Org. Chem.* **2009**, *6*, 219; b) A. Nishimura, E. Tamai, M. Ohashi, S. Ogoshi, *Chem. Eur. J.* **2013**, *19*, 6613; c) A. S. K. Hashmi, M. Wieteck, I. Braun, M. Rudolph, F. Rominger, *Angew. Chem. Int. Ed.* **2012**, *51*, 10633.

[27] a) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244; b) A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221; d) Z. Ni, L. Giordano, A. Tenaglia, *Chem. Eur. J.* **2014**, *20*, 11703.

Analizando la bibliografía observamos que los métodos fotoquímicos son minoritarios frente a aquellos catalizados por metales. De hecho, desde el año 2000 solo es posible encontrar unos cuantos trabajos experimentales[28] y teóricos.[29] Algunos ejemplos modernos del uso de irradiación para sintetizar ciclobutenos por cicloadición [2+2] se muestran en el Esquema II.12.



Esquema II.12

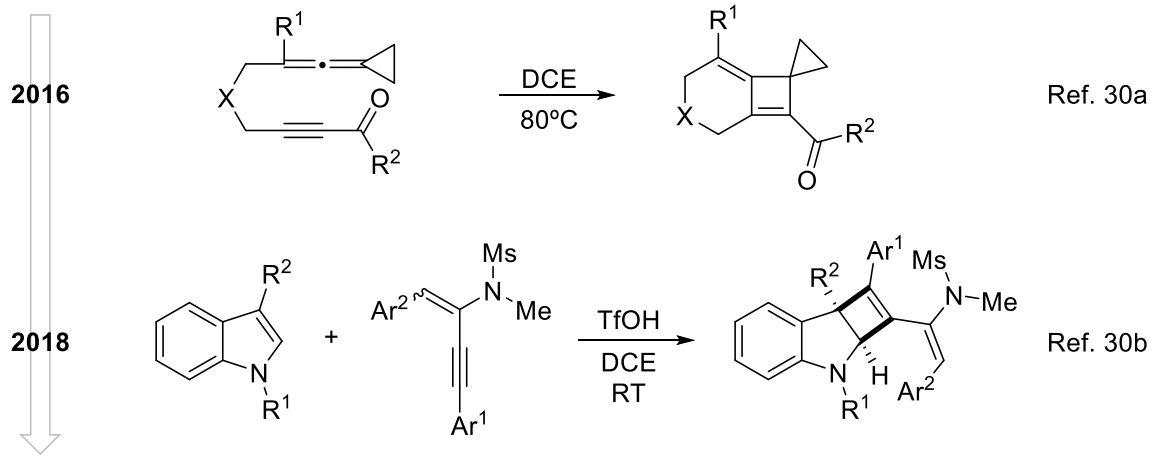
El último ejemplo del Esquema II.12 demuestra el enorme peso que tienen los metales en el campo de la síntesis de ciclobutenos, dado que hasta en algunos métodos fotoquímicos es necesario utilizar un catalizador fotorredox metálico. A los inconvenientes que presentan los métodos catalizados por metales se suma en

[28] a) R. Alibés, P. de March, M. Figueredo, J. Font, M. Racamonde, A. Rustullet, A. Alvarez-Larena, J. F. Piniella, T. Parella, *Tetrahedron Lett.* **2003**, *44*, 69; b) J. D. Winkler, E. C. McLaughlin, *Org. Lett.* **2005**, *7*, 2; c) S. Kulyk, W. G. Dougherty Jr. W. S. Kassel, S. A. Fleming, S. McN. Sieburth, *Org. Lett.* **2010**, *12*, 3296; d) A. Misale, S. Niyomchon, N. Maulide, *Acc. Chem. Res.* **2016**, *49*, 2444 e) J. Buendia, Z. Chang, H. Eijsberg, R. Guillot, A. Frongia, F. Secci, J. Xie, S. Robin, T. Boddaert, D. J. Aitken, *Angew. Chem.* **2018**, *130*, 1; f) A. Zech, T. Bach, *J. Org. Chem.* **2018**, *83*, 3069; g) G.-Q. Xu, J.-T. Xu, Z.-T. Feng, H. Liang, Z.-Y. Wang, Y. Qin, P.-F. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 5110.

[29] a) S. Sakai, *Chem. Phys. Lett.* **2000**, *319*, 687; b) H. Shi, D. C. Roettger, A. L. East, *J. Comput. Chem.* **2008**, *29*, 883; c) Y. Wang, K. B. Wiberg, *J. Phys. Chem. A* **2009**, *113*, 1686; d) W. Fuß., W. E. Schmid, S. A. Trushin, P. S. Billone, W. J. Leigh, *ChemPhysChem,* **2017**, *8*, 592.

estos casos la necesidad de un equipamiento especial para poder llevar a cabo las reacciones con luz.

Por ello, resulta tan importante buscar métodos que no requieran el uso de metales o luz. Evidentemente este es un reto importante y los trabajos publicados son muy escasos.[30] Un par de ejemplos seleccionados se muestran en el Esquema II.13. Sin embargo, estos métodos están limitados a sustratos muy específicos y se hace necesario el uso de ácidos fuertes o bien aplicar temperaturas altas.



Esquema II.13

Por tanto, se hace evidente que la evolución de estos métodos pasa por conseguir protocolos sin el uso de catalizadores u otros aditivos, ni irradiación, y todo ello a temperatura ambiente y en un solo paso de reacción. En los últimos años, nuestro grupo de trabajo ha hecho una aportación en este campo, al describir un método que cumple con todos estos requisitos y que, además, presenta una selectividad muy alta. Esta metodología será tratada en detalle en los Capítulos 1 y 2, así como en los apartados respectivos de la Discusión General de la presente Tesis Doctoral.

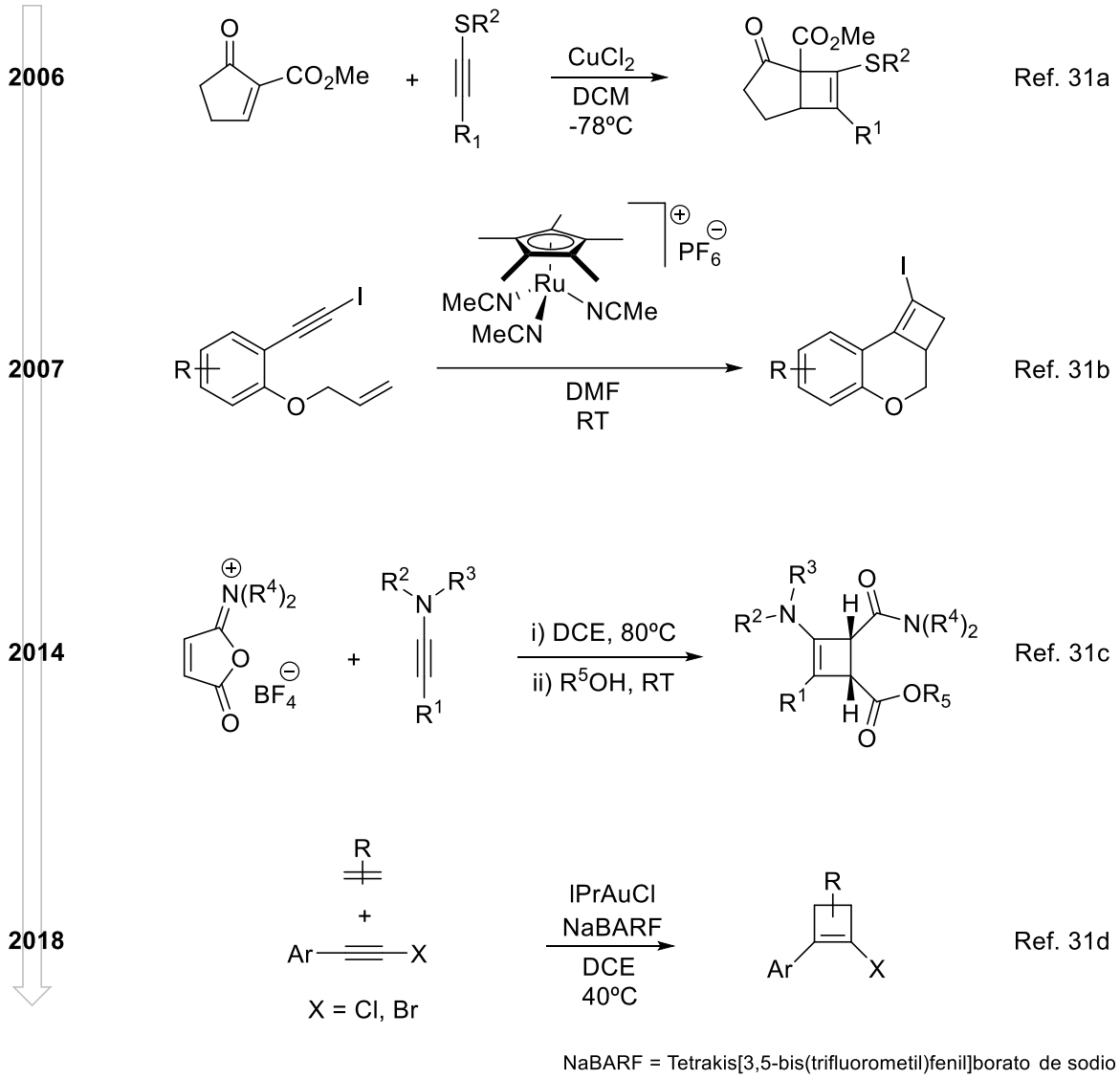
[30] a) S. Yang, Q. Xu, M. Shi, *Tetrahedron* **2016**, *72*, 584; b) T. R. Pradhan, H. W. Kim, J. K. Park, *Org. Lett.* **2018**, *20*, 5286.

II.2.2. Ciclobutenos heterosustituidos

Uno de los problemas más desafiantes en la síntesis de ciclobutenos es la introducción eficiente y selectiva de funcionalidades en el esqueleto carbocíclico de cuatro miembros.

Los ciclobutenos que presentan sustituyentes con heteroátomos (o grupos funcionales con heteroátomos) directamente unidos a un átomo de carbono sp^2 del carbociclo son muy interesantes, pues modulan directamente las propiedades físicas, químicas y biológicas, pero suponen un reto sintético adicional. Los heteroátomos, en ocasiones, modifican completamente el comportamiento de los materiales de partida provocando que métodos descritos no funcionen correctamente en estos sustratos, o que la reacción no sea controlable en términos de selectividad. Esto provoca que en muchas ocasiones se tenga que funcionalizar el ciclobuteno a *posteriori*, lo que supone más etapas sintéticas y una menor eficiencia. Para la formación de estos carbociclos heterosustituidos, se han seguido las estrategias anteriormente descritas (en las que predominan las de cicloadiciones [2+2]) pero introduciendo modificaciones de las condiciones de reacción para adaptarlas a cada sustrato concreto. Algunos ejemplos de metodologías de formación de ciclobutenos heterosustituidos[31] se muestran en el Esquema II.14.

[31] a) Y. Takenaka, H. Ito, M. Hasegawa, K. Iguchi, *Tetrahedron* **2006**, *62*, 3380; b) A. Fürstner, A. Schlecker, C. W. Lehmann, *Chem. Commun.* **2007**, 4277; c) Y. Yuan, L. Bai, J. Nan, J. Liu, X. Luan, *Org. Lett.* **2014**, *16*, 4316; d) Y.-B. Bai, Z. Luo, Y. Wang, J.-M. Gao, L. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 5860.



NaBARF = Tetrakis[3,5-bis(trifluorometil)fenil]borato de sodio

Esquema II.14

En esta muestra representativa, puede observarse como la estrategia [2+2] entre alquino y alqueno es predominante junto con el uso de metales. Solo el ejemplo del año 2014 muestra una metodología que no requiere el uso de catalizadores, pero necesita el uso de calor y está restringido a sustratos muy concretos. En nuestro caso, la metodología desarrollada es aplicable a una amplia variedad de sustratos heterosustituidos, aplicando las mismas condiciones de reacción independientemente de la naturaleza de estos y manteniendo las características tan ventajosas comentadas anteriormente. Todo ello será revisado en detalle en el Capítulo 2 y en su correspondiente apartado de la Discusión General.

II.2.3. Ciclobutenoles

Otro tipo de ciclobuteno importante son los ciclobutenoles. Estas estructuras cíclicas de cuatro eslabones presentan, además de un doble enlace, un grupo hidroxilo en su estructura (Figura II.6).

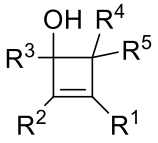


Figura II.6

Estos compuestos son materiales de partida altamente versátiles en Síntesis Orgánica ya que pueden transformarse fácilmente en una amplia gama de compuestos útiles.[32] Además, son elementos estructurales importantes en un gran número de compuestos biológicamente activos y productos naturales.[33] Sin embargo, los métodos sintéticos para su preparación son bastante limitados.[34] Por ejemplo, la ruta directa hacia los estos derivados de ciclobuteno a través de una cicloadición [2+2][35] de un alquino y una olefina vista anteriormente, no se puede utilizar, pues no permite introducir el grupo hidroxilo directamente en el anillo. La mayoría de los métodos descritos para acceder a los ciclobutenoles proceden a través de largas rutas sintéticas que implican un paso de reducción o adición nucleófila al carbonilo de una ciclobutenona.[34a] Además, el control de la selectividad durante la formación de las ciclobutenonas es un desafío,[36] y hasta la fecha, solo se conocen unos pocos métodos para la síntesis de ciclobutenoles por métodos alternativos en varias etapas.[34b,d] De hecho el método que hemos descrito en el Capítulo 3 a partir de inamidas es el primero que permite acceder a ciclobutenoles

[32] a) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485; b) A. Misale, S. Niyomchon, N. Maulide, *Acc. Chem. Res.* **2016**, *49*, 2444.

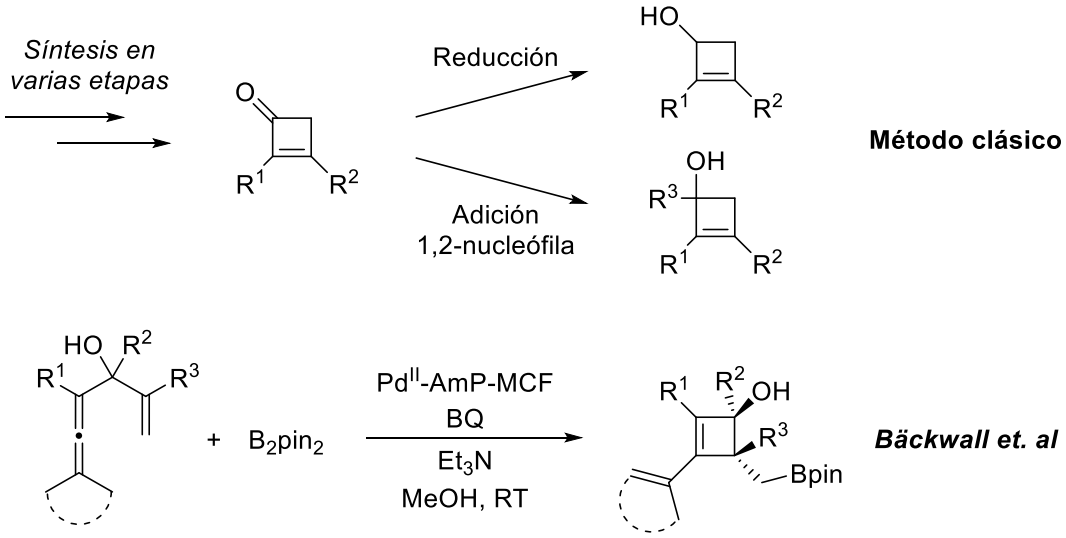
[33] V. M. Dembitsky, *J. Nat. Med.* **2007**, *62*, 1.

[34] a) A. A. Frimer, H. Pizem, *Tetrahedron* **1999**, *55*, 12175; b) C. M. Gampe, S. Boulos, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 4092; c) C. M. Gampe, E. M. Carreira, *Chem. Eur. J.* **2012**, *18*, 15761; d) B. Darses, A. E. Greene, J.-F. Polsson, *Org. Lett.* **2010**, *12*, 3994; e) S. Yang, W. Yuan, Q. Xu, M. Shi, *Chem. Eur. J.* **2015**, *21*, 15964.

[35] a) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449; b) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 11918.

[36] G. Chai, S. Wu, C. Fu, S. Ma, *J. Am. Chem. Soc.* **2011**, *133*, 3740.

en un solo paso, sin necesidad de sintetizar una ciclobutenona intermedia. Recientemente, el grupo de Bäckwall también ha conseguido un método directo para sintetizar ciclobutenoles diastereoselectivamente a partir de alenoles[37] (Esquema II.15).



Esquema II.15

Por lo tanto, el desarrollo de nuevos métodos eficientes para la síntesis de ciclobutenoles es una tarea importante para poder ofrecer herramientas alternativas a la hora de afrontar su síntesis.

[37] M.-B. Li, D. Posevins, K. P. J. Gustafson, C.-W. Tai, A. Shchukarev, Y. Qiu, J.-E. Bäckvall, *Chem. Eur. J.* **2019**, *25*, 210.

II.3. Ciclobutenonas:

Las ciclobutenonas son cetonas α,β-insaturadas cíclicas de cuatro miembros (Figura II.7).

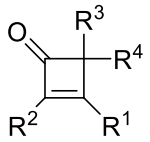


Figura II.7

Como ocurre con ciclobutenos y ciclobutenoles, las ciclobutenonas poseen una inherente tensión de anillo que les proporciona una alta reactividad. Además, se suma la presencia de un grupo carbonilo en su estructura, lo que abre la puerta a una mayor diversidad de reacciones.[38] Las ciclobutenonas son estructuras que experimentan fácilmente apertura de anillo bajo una variedad de condiciones, incluyendo la termólisis,[39] la fotólisis[40] y la catálisis con metales de transición,[41] para

[38] a) T. Kondo, T.-A. Mitsudo, *Chem. Lett.* **2005**, *34*, 1462; b) R. Martin, A. Flores-Gaspar, *Synthesis* **2013**, 563; c) P.-H. Chen, G. Dong, *Chem. Eur. J.* **2016**, *22*, 18290.

[39] a) H. W. Moore, O. H. W. Decker, *Chem. Rev.* **1986**, *86*, 821; b) W. R. Dolbier Jr. H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471; b) S. Niwayama, E. A. Kallel, C. M. Sheu, K. N. Houk, *J. Org. Chem.* **1996**, *61*, 2517.

[40] a) J. E. Baldwin, C. Mcdaniel, *J. Am. Chem. Soc.* **1967**, *89*, 1537; b) J. E. Baldwin, M. C. Mcdaniel, *J. Am. Chem. Soc.* **1968**, *90*, 6118; c) O. L. Chapman, J. D. Lassila, *J. Am. Chem. Soc.* **1968**, *90*, 2449; d) F. Toda, E. Todo, *Chem. Lett.* **1974**, 1279; e) F. Toda, E. Todo, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2503; f) F. Toda, Y. Todo, E. Todo, Bull. *Chem. Soc. Jpn.* **1976**, *49*, 2645; g) O. Kikuchi, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1669;

[41] a) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1990**, *112*, 8617; b) M. A. Huffman, L. S. Liebeskind, W. T. Pennington, *Organometallics* **1990**, *9*, 2194; c) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1991**, *113*, 2771; d) M. A. Huffman, L. S. Liebeskind, W. T. Pennington, *Organometallics* **1992**, *11*, 255; e) M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1993**, *115*, 4895; f) T. Kondo, Y. Taguchi, Y. Kaneko, M. Niimi, T. A. Mitsudo, *Angew. Chem. Int. Ed.* **2004**, *43*, 5369; g) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932; h) T. Kondo, M. Niimi, M. Nomura, K. Wada, T. A. Mitsudo, *Tetrahedron Lett.* **2007**, *48*, 2837; i) A. L. Auvinet, J. P. Harrity, *Angew. Chem. Int. Ed.* **2011**, *50*, 2769; j) T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2012**, *51*, 7567; k) T. Xu, H. M. Ko, N. A. Savage, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 20005; l) Y. Masuda, M. Hasegawa, M. Yamashita, K. Nozaki, N. Ishida, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 7142; m) T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2014**, *53*, 10733; n) T. Xu, N. A. Savage, G. Dong, *Angew. Chem. Int. Ed.* **2014**, 53, 1891; o) P. H. Chen, T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2014**, *53*, 1674; p) L. Souillart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410; q) T. Stalling, W. R. Harker, A. L. Auvinet, E. J. Cornel, J. P. Harrity, *Chem. Eur. J.* **2015**, *21*, 2701; r) G. Lu, C. Fang, T. Xu, G. Dong, P. Liu, *J. Am. Chem. Soc.* **2015**, *137*, 8274; s) F. Juliá-Hernández, A. Ziadi, A. Nishimura, R. Martin, *Angew. Chem. Int. Ed.* **2015**, *54*, 9537; t) X. Zhou, I. Zafar, G. Dong, *Tetrahedron* **2015**, *71*, 4478; u) X.-F. Fu, Y. Xiang, Z.-X. Yu, *Chem. Eur. J.* **2015**, *21*, 4242;

proporcionar intermedios reactivos que se pueden atrapar con nucleófilos[42] y sistemas insaturados.[43] Al ser enonas deficientes en electrones son buenos electrófilos frente a la adición nucleófila 1,2 o 1,4[44] y también pueden actuar como dienófilos.[45] Tales propiedades les confieren una reactividad única y convierten a esta estructura en un sintón extremadamente versátil, sirviendo como excelentes sustratos en una amplia gama de transformaciones sintéticamente valiosas (Esquema II.16).

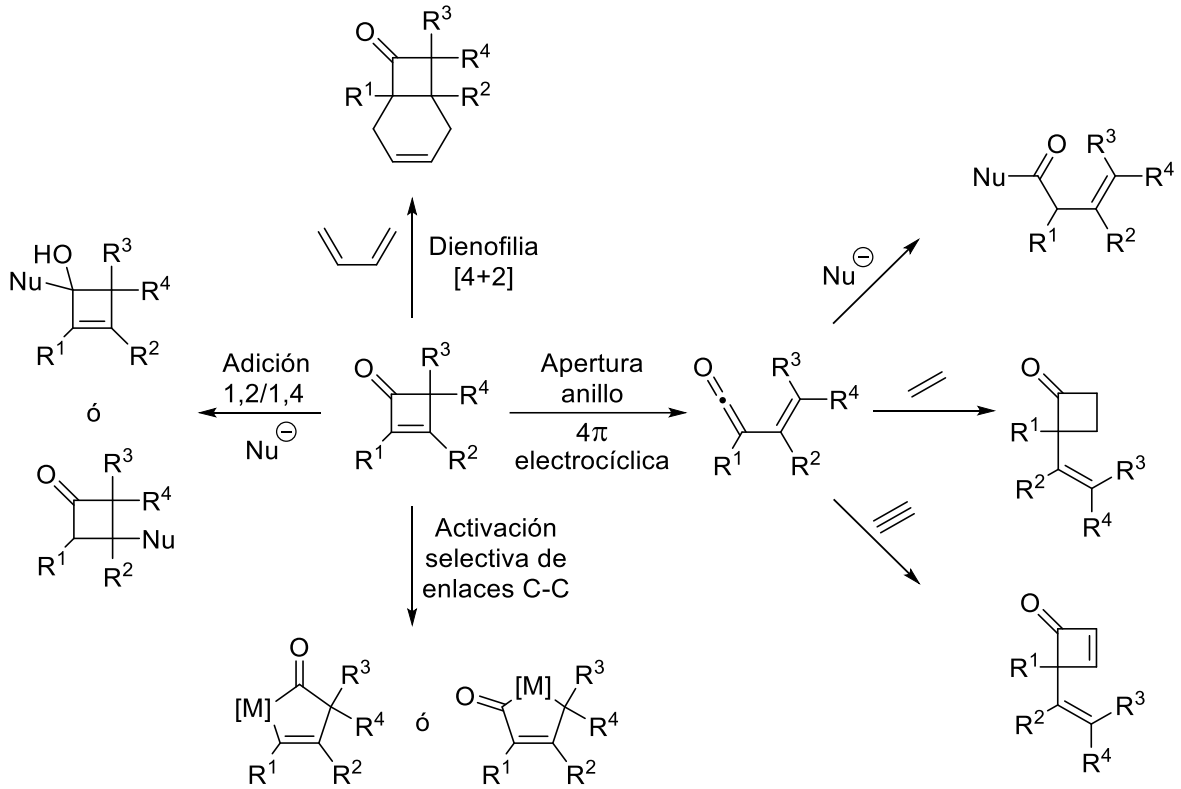
v) Y.Wang, Z.-X. Yu, *Acc. Chem. Res.* **2015**, *48*, 2288; w) P.-H. Chen, J. Sieber, C. H. Senanayake, G. Dong, *Chem. Sci.* **2015**, *6*, 5440; x) L. Deng, T. Xu, H. Li, G. Dong, *J. Am. Chem. Soc.* **2016**, *138*, 369.

[42] a) E. F. Jenny, J. D. Roberts, *J. Am. Chem. Soc.* **1956**, *78*, 2005; b) R. Huisgen, H. Mayr, *J. Chem. Soc. Chem. Commun.* **1976**, 55.

[43] a) H. Mayr, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 500; b) J. Ficini, S. Falou, J. Dangelo, *Tetrahedron Lett.* **1977**, *18*, 1931; c) R. L. Danheiser, S. K. Gee, H. Sard, *J. Am. Chem. Soc.* **1982**, *104*, 7670; d) R. L. Danheiser, S. K. Gee, J. Org. Chem. **1984**, *49*, 1672; e) R. L. Danheiser, S. K. Gee, J. J. Perez, *J. Am. Chem. Soc.* **1986**, *108*, 806; f) C. J. Kowalski, G. S. Lal, *J. Am. Chem. Soc.* **1988**, *110*, 3693; g) R. L. Danheiser, A. Nishida, S. Savariar, M. P. Trova, *Tetrahedron Lett.* **1988**, *29*, 4917; h) X. Y. Mak, A. L. Crombie, R. L. Danheiser, *J. Org. Chem.* **2011**, *76*, 1852.

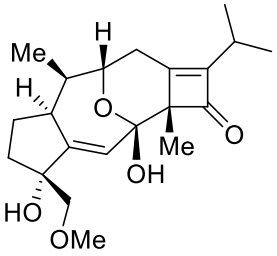
[44] a) J. D. Roberts, G. B. Kline, H. E. Simmons, *J. Am. Chem. Soc.* **1953**, *75*, 4765; b) E. F. Silversmith, J. D. Roberts, *J. Am. Chem. Soc.* **1956**, *78*, 4023; c) E. F. Silversmith, Y. Kitahara, M. C. Caserio, J. D. Roberts, *J. Am. Chem. Soc.* **1958**, *80*, 5840; d) M. P. Cava, K. Muth, *J. Am. Chem. Soc.* **1960**, *82*, 652; e) A. Hassner, J. L. Dillon, *J. Org. Chem.* **1983**, *48*, 3382; f) A. Cammers-Goodwin, *J. Org. Chem.* **1993**, *58*, 7619; g) J. C. Bradley, T. Durst, *Can. J. Chem.* **1995**, *73*, 1660; h) T. Matsumoto, T. Hamura, Y. Kuriyama, K. Suzuki, Tetrahedron Lett. **1997**, *38*, 8985; i) A. Gokhale, P. Schiess, Helv. *Chim. Acta* **1998**, 81, 251; j) M. Murakami, Y. Miyamoto, Y. Ito, *Angew. Chem. Int. Ed.* **2001**, *40*, 189; k) M. Murakami, Y. Miyamoto, Y. Ito, *J. Am. Chem. Soc.* **2001**, *123*, 6441; l) N. A. Magomedov, P. L. Ruggiero, Y. Tang, *J. Am. Chem. Soc.* **2004**, *126*, 1624; m) Y. Matsuya, N. Ohsawa, H. Nemoto, *J. Am. Chem. Soc.* **2006**, *128*, 13072; n) Y. Matsuya, H. Katayanagi, T. Ohdaira, Z. L. Wei, T. Kondo, H. Nemoto, *Org. Lett.* **2009**, *11*, 1361; o) P. García-García, C. Novillo, M. A. Fernández-Rodríguez, E. Aguilar, *Chem. Eur. J.* **2011**, *17*, 564; p) K. Sugimoto, R. Hayashi, H. Nemoto, N. Toyooka, Y. Matsuya, *Org. Lett.* **2012**, *14*, 3510 q) Y. Li, X. Su, W. Zhou, W. Li, J. Zhang, *Chem. Eur. J.* **2015**, *21*, 4224; r) B. S. Li, Y. Wang, Z. Jin, P. Zheng, R. Ganguly, Y. R. Chi, *Nat. Commun.* **2015**, *6*, 6207; s) B.-S. Li, Y. Wang, Z. Jin, Y. R. Chi, *Chem. Sci.* **2015**, *6*, 6008.

[45] a) T. R. Kelly, R. W. Mcnutt, *Tetrahedron Lett.* **1975**, *16*, 285; b) B. Bienfait, G. Coppemotte, R. Merenyi, H. G. Viehe, W. Sicking, R. Sustmann, *Tetrahedron* **1991**, *47*, 8167; c) X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 11004; d) H. V. Pham, R. S. Paton, A. G. Ross, S. J. Danishefsky, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 2397.



Esquema II.16

Aunque no se conocen muchos productos naturales que incorporen el núcleo de ciclobutenona, recientemente se ha descubierto el Alterbrassiceno A que la contiene.[46] Es un metabolito extraído de la *Alternaria Brassicicola* que presenta una potente actividad inhibidora de IKKβ en la vía de señalización de NF-κB (Figura II.8).

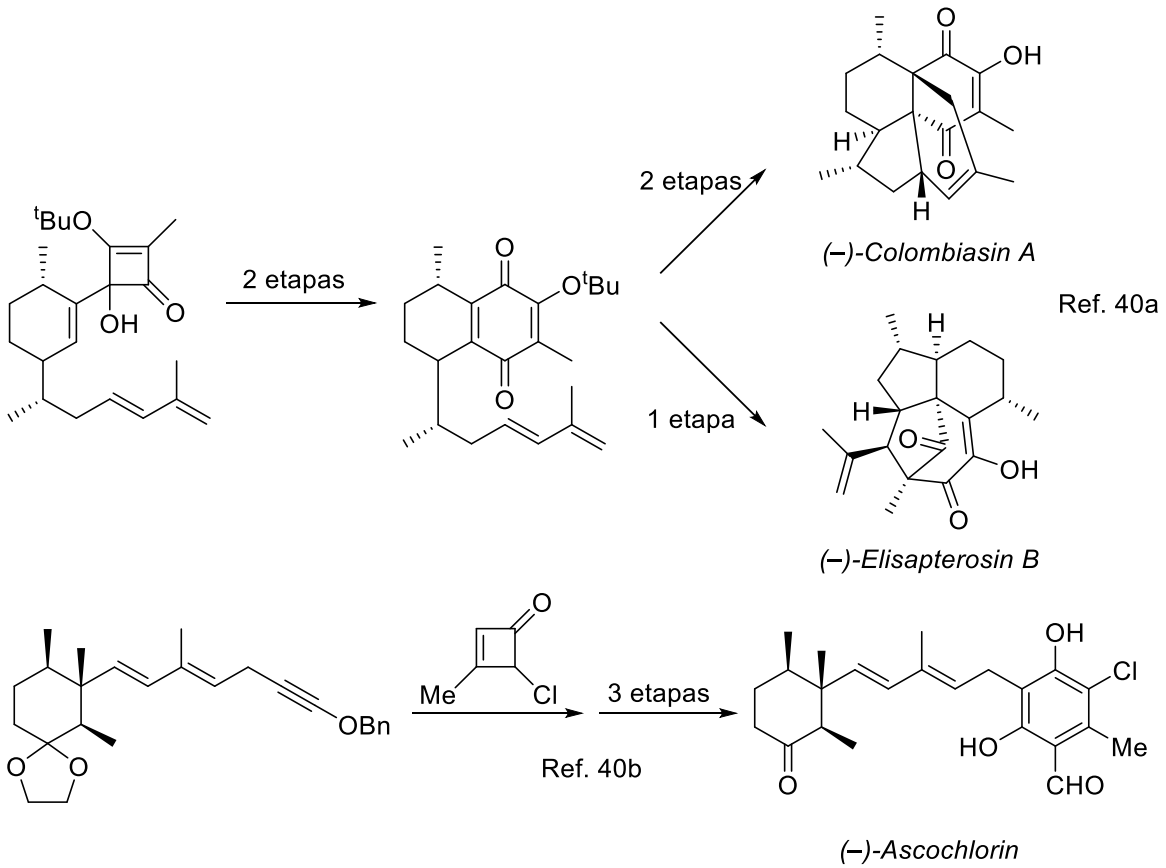


Alterbrassiceno A

Figura II.8

[46] a) D. Bellus, B. Ernst, *Angen. Chem. Int. Ed. Engl.* **1988**, *27*, 79; b) Z. Hu, W. Sun, F. Li, J. Guan, Y. Lu, J. Liu, Y. Tang, G. Du, Y. Xue, Z. Luo, J. Wang, H. Zhu, Y. Zhang, *Org. Lett.* **2018**, *20*, 5198; c) R. A. Hill, A. Sutherland, *Nat. Prod. Rep.* **2018**, *35*, 1236.

Aunque la presencia del anillo ciclobutenona en compuestos naturales es limitada, resulta clave en las rutas de síntesis de laboratorio de muchos de ellos. Un par de ejemplos[47] interesantes se recogen en el Esquema II.17.

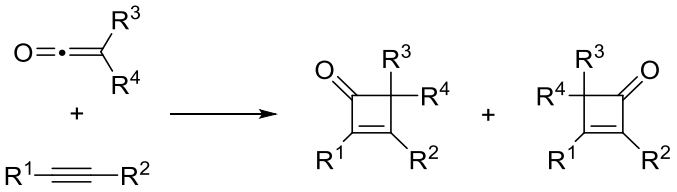


Esquema II.17

El método clásico y más extendido para la síntesis del esqueleto de ciclobutenona aprovecha la reacción de cicloadición [2+2] entre alquinos y cetenas generadas *in situ*[48] (Esquema II.18).

[47] a) D. C. Harrowven, D. D. Pascoe, D. Demurtas, H. O. Bourne, *Angew. Chem. Int. Ed.* **2005**, *44*, 1221; b) G. B. Dudley, K. S. Takaki, D. D. Cha, R. L. Danheiser, *Org. Lett.* **2000**, *2*, 21.

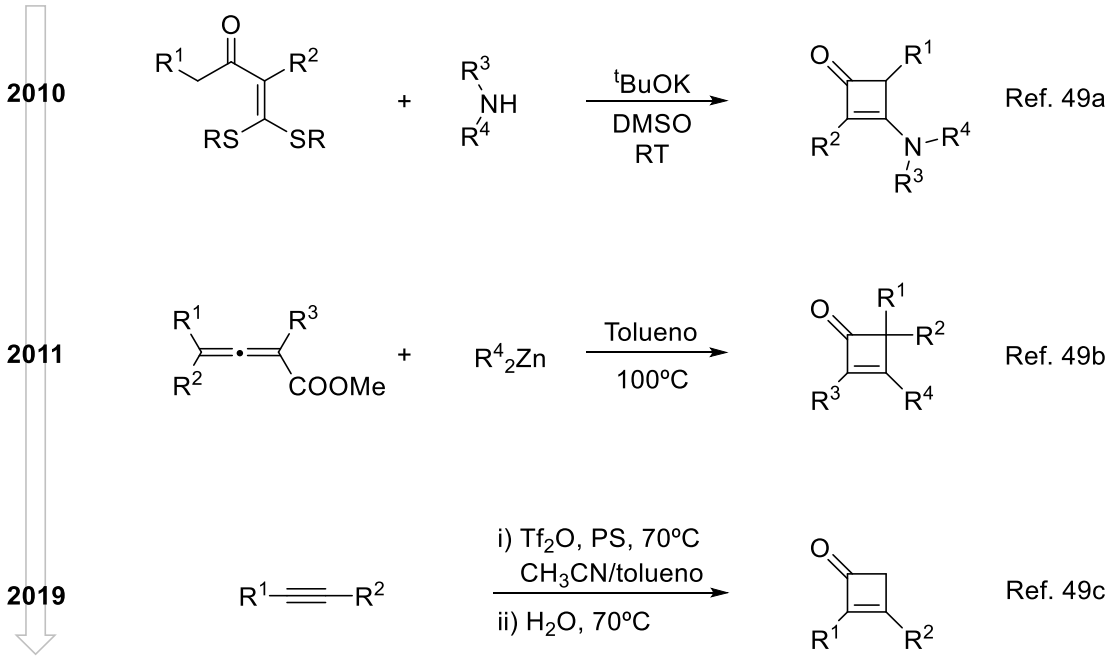
[48] a) R. L. Danheiser, S. Savariar, D. D. Cha, *Org. Synth.* **1990**, *68*, 32; b) *In Organic Reactions, 1ª ed.,* J. A. Hyatt, P. W. Raynolds, L. A. Paquette, Wiley, Nueva York, EEUU, **1994**; c) *In Science of Synthesis: Houben Weyl Methods of Molecular Transformations, 1ª ed., Vol. 23,* R. L. Danheiser, D. Bellus, Thieme, Stuttgart, Alemania, **2006**.



Esquema II.18

Sin embargo, los rendimientos de este tipo de reacciones no suelen ser muy altos y en muchas ocasiones son necesarios varios pasos adicionales para llegar a la ciclobutenona deseada. Además, pueden darse problemas de regioselectividad durante la reacción de formación del anillo, originando mezcla de isómeros.

Fuera de este método clásico encontramos escasísimos ejemplos de otras estrategias para la formación de estas enonas cíclicas. De hecho, en los últimos 20 años, se han publicado muy pocas metodologías nuevas[49] (Esquema II.19).



Esquema II.19

[49] a) Y.-L. Zhao, S.-C. Yang, C.-H. Di, X.-D. Han, Q. Liu, *Chem. Commun*. **2010**, *46*, 7614; b) G. Chai, S. Wu, C. Fu, S. Ma, *J. Am. Chem. Soc.* **2011**, *133*, 3740; c) Q. Qin, X. Luo, J. Wei, Y. Zhu, X. Wen, S. Song, N. Jiao, *Angew. Chem. Int. Ed.* **2019**, *58*, 4376.

En consecuencia, el desarrollo de nuevos métodos para la síntesis controlada de ciclobutenonas es de marcada importancia, dada la escasez de herramientas disponibles para su obtención.

II.4. Flavonoides

Los flavonoides son una clase de metabolitos secundarios de origen vegetal con estructuras fenólicas muy variadas. Se encuentran en frutas, verduras, granos, corteza, raíces, tallos, flores, té y vino. Estos productos naturales son bien conocidos por sus efectos beneficiosos para la salud y se realizan grandes esfuerzos en su aislamiento. Han alcanzado tal grado de importancia que se consideran un componente indispensable en una variedad de aplicaciones nutricionales, farmacéuticas, medicinales y cosméticas. Esto se atribuye a sus propiedades antioxidantes, antiinflamatorias, antimutagénicas, anticancerígenas, antidiabéticas y cardioprotectoras, junto con su capacidad para modular la función de enzimas clave.[50]

La tendencia actual en este campo de investigación se centra en el aislamiento, la identificación, la caracterización, la determinación de sus funciones y sus posibles aplicaciones. Dentro de estas actividades, la síntesis de estas estructuras juega un papel fundamental como herramienta para su producción y comercialización, así como para conseguir estructuras relacionadas de diseño, no presentes en la naturaleza, pero diseñadas para una diana específica.

Sus estructuras básicas consisten en anillos C6-C3-C6 con multitud de patrones de sustitución, lo que da origen a diferentes familias y subclases de compuestos. Son moléculas con una fuerte correlación entre sus estructuras químicas y bioactividades. En la Figura II.9 se recogen las principales familias de compuestos considerados flavonoides.

[50] a) A. R. Tapas, D. M. Sakarkar, R. B. Kakdea, *Trop. J. Pharm. Res.* **2008**, *7*, 1089; b) A. N. Panche, A. D. Diwan, S. R. Chandra, *J. Nutr. Sci.* **2016**, *5*, E47; c) K. Pallauf, N. Duckstein, G. Rimbach, *P. Nutr. Soc.* **2017**, *76*, 145; d) T.-Y. Wang, Q. Li, K.-S. Bi, *Asian J. Pharm. Sci.* **2018**, *13*, 12.

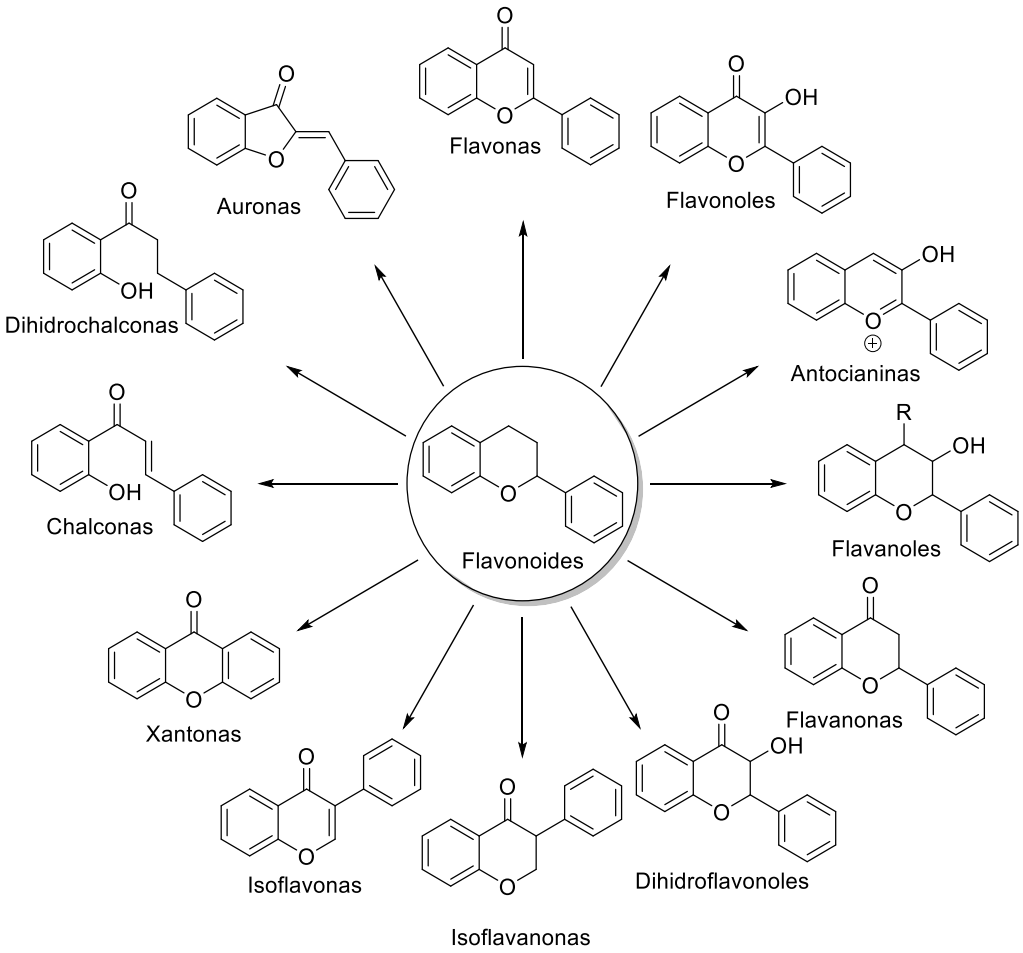


Figura II.9

II.4.1. Flavonas

Las flavonas son una familia de compuestos dentro del grupo de los flavonoides. Son heterociclos oxigenados que se diferencian de otros flavonoides en que tienen un doble enlace entre C2 y C3 en el esqueleto base, no hay sustitución en la posición C3 y la posición C4 se encuentra oxidada. Es decir, son estructuras basadas en el núcleo de cromona sustituidas en posición C2 (Figura II.10).

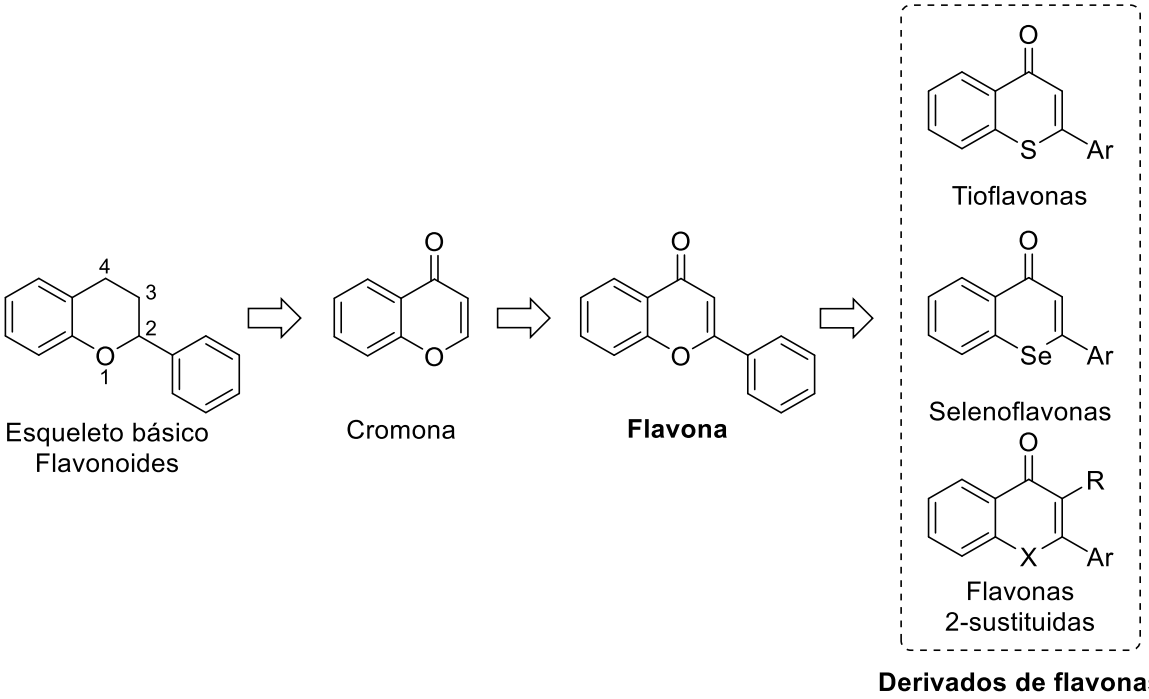


Figura II.10

La derivatización del núcleo de flavona ha originado multitud de estructuras. Esta Tesis se ha centrado principalmente en flavonas funcionalizadas en la posición C3, así como en las que el átomo de oxígeno de la posición 1 se ha sustituido por elementos equivalentes del grupo de los anfígenos, como azufre (tioflavonas) y selenio (selenoflavonas), (Figura II.10).

Las flavonas, como el resto de flavonoides, son de origen vegetal y presentan importantes funciones biológicas y aplicaciones farmacológicas. La gran diversidad de estructuras derivadas de este núcleo le otorga su amplia gama de actividades. La relación actividad-estructura que presentan ha dado lugar a un gran número de investigaciones que han culminado en el descubrimiento de diferentes moléculas para el tratamiento de numerosas enfermedades (Figura II.11).

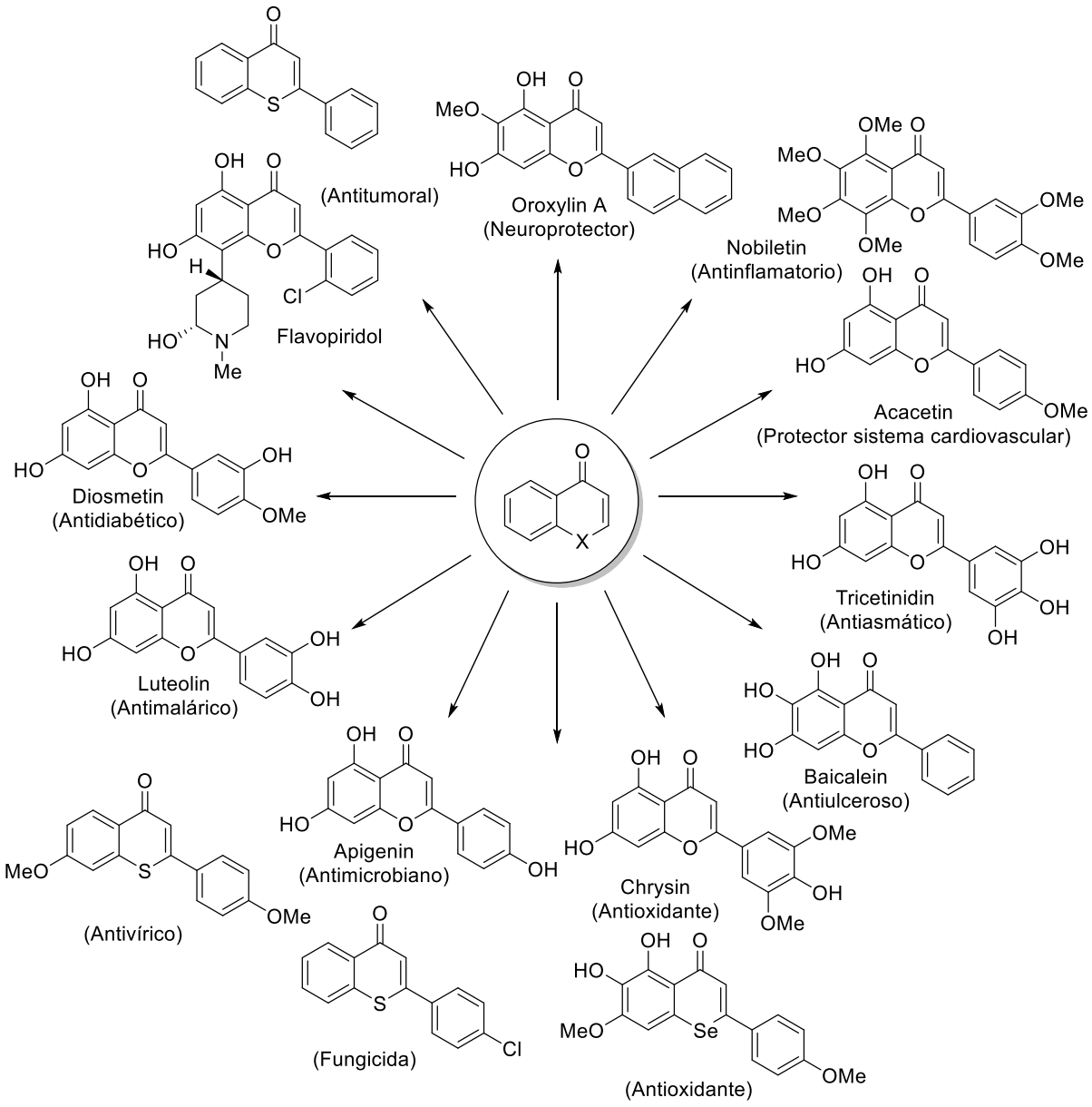


Figura II.11

La evidente importancia de estos compuestos ha impulsado el desarrollo de nuevos procedimientos y la modificación de otros ya existentes para la obtención de estos aductos. Las flavonas se pueden preparar mediante varios métodos sintéticos clásicos, por ejemplo, a partir de *orto*-hidroxiarilcetonas, mediante condensación de

Claisen,[51] reagrupamiento de Baker-Venkataraman,[52] síntesis por vía Kostanecki-Robinson, [53] reacción de Vilsmeier-Haack [54] y síntesis a través de sales de benzopirilio[55] (Esquema II.20).

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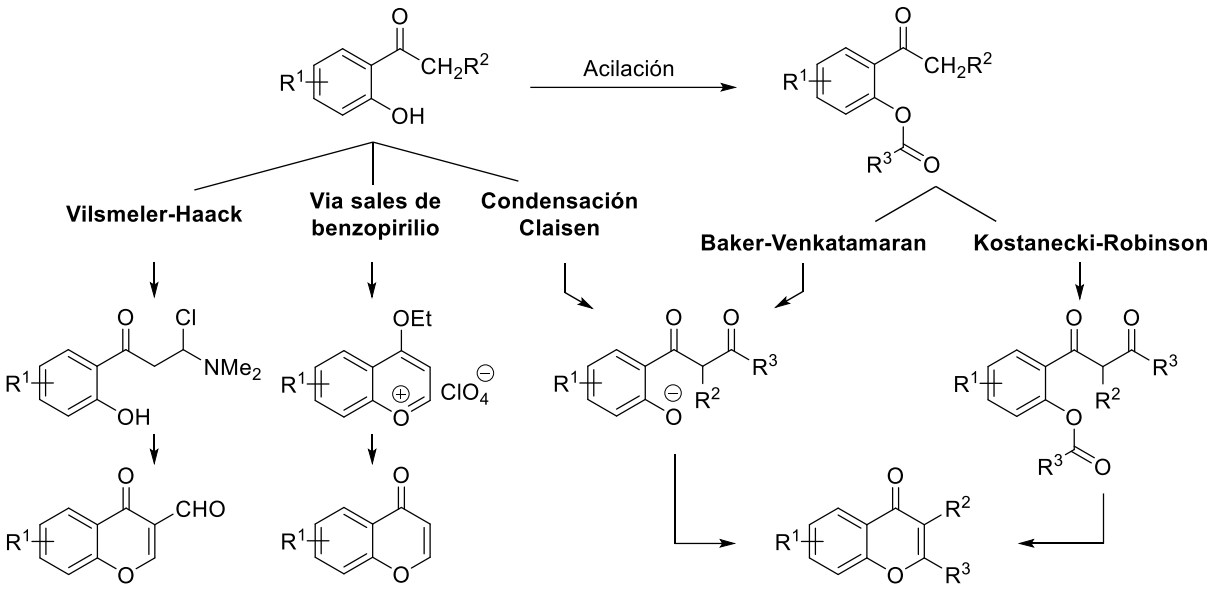


Esquema II.20

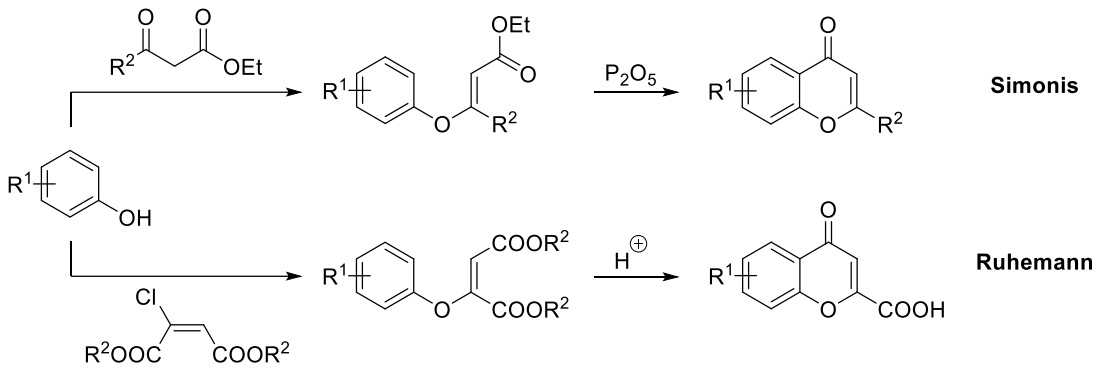
Utilizando como materiales de partida fenoles encontramos dos métodos, la síntesis vía reacción de Simonis[56] y reacción de Ruhemann[57] (Esquema II.21).

[54] a) A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron Lett.* **1973**, *14*, 1995; b) G. Sabitha, *Aldrichim. Acta* **1996**, *29*, 13; c) A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron* **1974**, *30*, 3553; d) T. Högberg, M. Vora, S. D. Drake, L. A. Mitscher, D. T. W. Chu, *Acta Chem. Scand.* **1984**, *38*, 359; e) J. Morris, D. G. Wishka, Y. Fang, *J. Org. Chem.* **1992**, *57*, 6502; f) Y. Ichiro, M. Keiko, S. Yoshiaki, H. Tsutomu, S. Yoshiaki, *Chem. Pharm. Bull.* **1994**, *42*, 1697; g) J. I. Borrell, J. Teixidó, E. Schuler, E. Michelotti, *Tetrahedron Lett.* **2001**, *42*, 5331; h) M. M. Ali, S. Sana, K. C. Rajanna, P. K. Saiprakash, *Synth. Commun.* **2002**, *32*, 1351; i) J. Alderete, J. Belmar, M. Parra, C. Zúñiga, V. Jimenez, *Liq. Cryst.* **2003**, *30*, 1319; j) V. Y. Sosnovskikh, *Russ. Chem. Rev.* **2003**, *72*, 489; c) O. Prakash, R. Kumar, D. Sharma, V. Bhardwaj, *J. Indian Chem. Soc.* **2004**, *81*, 888; k) D. A. Vasselin, A. D. Westwell, C. S. Matthews, T. D. Bradshaw, M. F. G. Stevens, *J. Med. Chem.* **2006**, *49*, 3973; l) W. K. Su, Z. H. Li, L. Y. Zhao, *Org. Prep. Proced. Int.* **2007**, *39*, 495; m) W. K. Su, X. Y. Zhu, Z. H. Li, *Org. Prep. Proced. Int.* **2009**, 41, 69.

[55] a) G. N. Dorofeenko, V. V. Tkachenko, *Chem. Heterocycl. Compd.* **1972**, *8*, 935; b) J. C. Jaen, L. D. Wise, T. G. Heffner, T. A. Pugsley, L. T. J. Meltzer, *Med. Chem.* **1991**, *34*, 248; c) J. Bolós, S. Gubert, L. Anglada, J. M. Planas, C. Burgarolas, J. M. Castelló, A. Sacristán, J. A. Ortiz, *J. Med. Chem.* **1996**, *39*, 2962; d) T. Inaba, K. Tanaka, R. Takeno, H. Nagaki, C. Yoshida, S. Takano, *Chem. Pharm. Bull.* **2000**, *48*, 131; e) M. Lubbe, B. Appel, A. Flemming, C. Fischer, P. Langer, *Tetrahedron* **2006**, *62*, 11755;

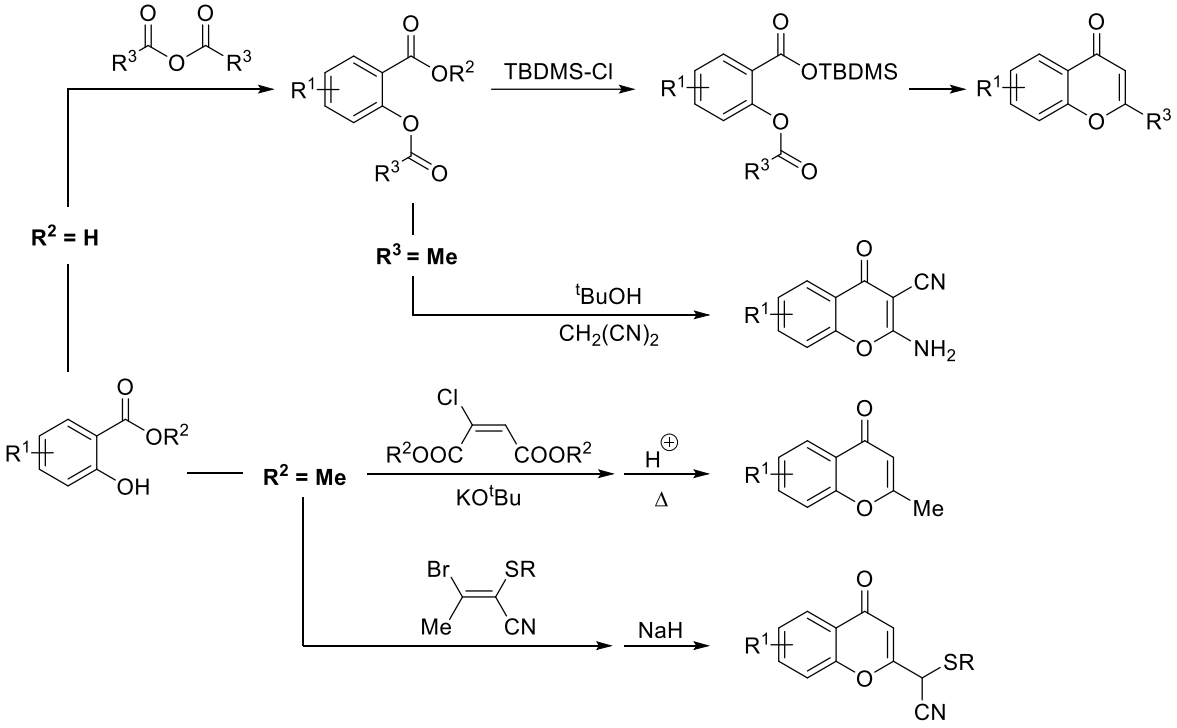
[56] a) M. Mazzei, A. Balbi, G. Roma, M. Di Braccio, G. Leoncini, E. Buzzi, M. Maresca, *Eur. J. Med. Chem.* **1988**, *23*, 237; b) M. Mazzei, E. Sottofattori, M. Di Braccio, A. Balbi, G. Leoncini, E. Buzzi, M. Maresca, *Eur. J. Med. Chem.* **1990**, *25*, 617; c) U. Oyman, K. Gunaydin, *Bull. Soc. Chim. Belg.* **1994**, *103*, 763; d) L. Costantino, G. Rastelli, M. C. Gamberini, J. A. Vinson, P. Bose, A. Iannone, M. Staffieri, L. Antolini, A. Del Corso, U. Mura, A. Albasini, *J. Med. Chem.* **1999**, *42*, 1881; e) E. Fillion, A. M. Dumas, B. A. Kuropatwa, N. R. Malhotra, T. C. Sitler, *J. Org. Chem.* **2005**, *71*, 409.

[57] D. Obrecht, *Helv. Chim. Acta* **1989**, *72*, 447.



Esquema II.21

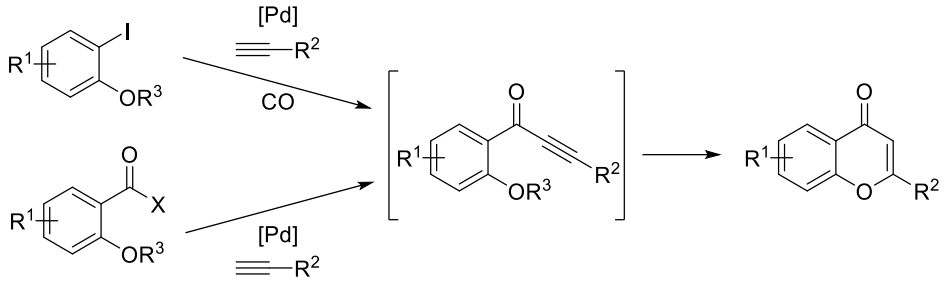
Otros materiales de partida muy utilizados son el ácido salicílico y sus derivados[58] (Esquema II.22).



Esquema II.22

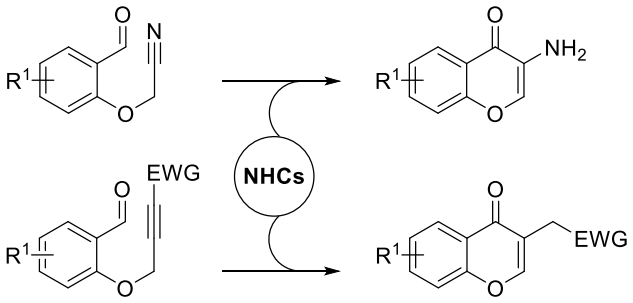
[58] a) N. S. Nixon, F. Scheinmann, J. L. Suschitzky, *Tetrahedron Lett.* **1983**, *24*, 597; b) F. Pochat, P. L'Haridon, *Synth. Commun.* **1998**, *28*, 957; c) P. Kumar, M. S. Bodas, *Org. Lett.* **2000**, *2*, 3821; d) J.-C. Jung, J.-P. Min, O.-S. Park, *Synth. Commun.* **2001**, *31*, 1837; e) G. Athanasellis, G. Melagraki, A. Afantitis, K. Makridima, O. Igglessi-Markopoulou, *Arkivoc* **2006**, *10*, 28.

Por supuesto, los procesos catalizados por metales también están presentes en la formación de flavonas. Principalmente, el paladio es protagonista en este tipo de procesos[59] (Esquema II.23).



Esquema II.23

Tambien existen métodos catalizados por organocatalizadores, utilizando carbenos *N*-heterocíclicos (NHCs)[60] (Esquema II.24).



Esquema II.24

El uso de cromanonas para obtener el núcleo de cromona presente en las flavonas no es tan común como los métodos anteriores ya que, en general, los rendimientos que ofrecen suelen ser bajos.[61]

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[59] a) V. N. Kalinin, M. V. Shostakovsky, A. B. Ponomaryov, *Tetrahedron Lett.* **1990**, *31*, 4073; b) C.-F. Lin, W.-D. Lu, I. W. Wang, M.-J. Wu, *Synlett* **2003**, *13*, 2057; c) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 6097; d) E. Awuah, A. Capretta, *Org. Lett.* **2009**, *11*, 3210; e) Q. Yang, H. Alper, *J. Org. Chem.* **2010**, *75*, 948;

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Como ocurre con muchas clases de compuestos, en multitud de ocasiones, no es posible obtener directamente la molécula deseada y se han de realizar pasos de reacción adicionales tras la formación del núcleo para llegar a la estructura final. Por ello, muchas flavonas funcionalizadas se obtienen a partir de otras flavonas precursoras. Casos típicos son aquellos en los que la flavona final contiene un heterociclo,[62] que se forma tras la construcción del núcleo de cromona.

El gran número de protocolos existente demuestra el enorme interés que suscitan estos compuestos; tendencia que no ha hecho más que crecer en los últimos años, lo que se refleja en la publicación de nuevos métodos sintéticos que mejoren a los anteriores en rendimiento y alcance.[63] Aun así, los métodos clásicos vistos anteriormente siguen siendo muy utilizados, muchos de ellos a escala industrial, por lo que la mayoría de métodos nuevos son mejoras de los anteriores mediante el uso de la tecnología actual, como las síntesis promovidas por microondas y el uso de catalizadores más sofisticados.

Sin embargo, la mayoría de estos métodos, no pueden extenderse a la síntesis de tioflavonas o selenoflavonas ni a la síntesis de flavonas funcionalizadas

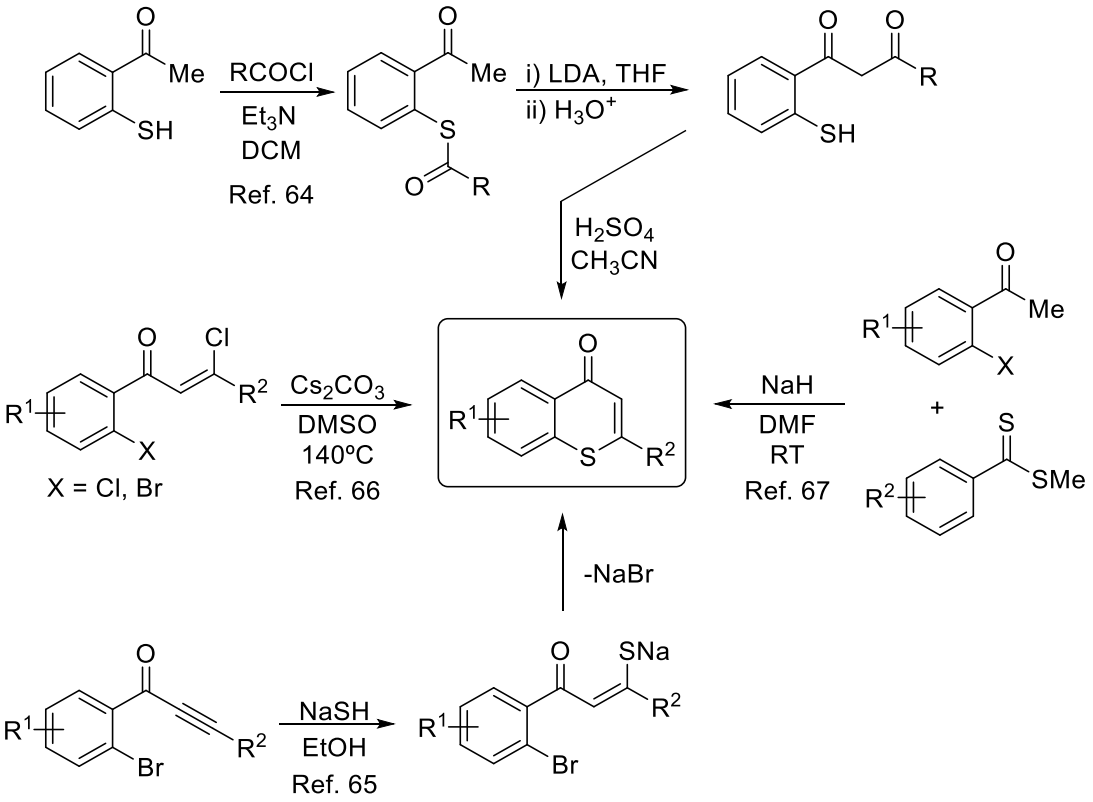
2227; a) D. S. Clarke, C. D. Gabbutt, J. D. Hepworth, B. M. Heron, *Tetrahedron Lett.* **2005**, *46*, 5515; a) V. Y. Sosnovskikh, R. A. Irgashev, *Synlett* **2005**, *7*, 1164; b) V. Y. Sosnovskikh, R. A. Irgashev, M. A. Barabanov, *Synthesis* **2006**, *16*, 2707; a) M. Fridén-Saxin, N. Pemberton, K. Silva Andersson, C. Dyrager, A. Friberg, M. Grøtli, K. Luthman, *J. Org. Chem.* **2009**, *74*, 2755.

62 a) H. M. El-Shaaer, P. Foltínová, M. Lácová, J. Chovancová, H. Stankovičová, *Farmaco* **1998**, *53*, 224; a) L. Tsao, L. Chzhan, T. Lyu, *Chem. Nat. Compd.* **2001**, *37*, 311; a) L. Cao, W. Wang, *Chem. Heterocycl. Compd.* **2003**, *39*, 1072; a) L. Cao, L. Zhang, J. Liu, *J. Chem. Heterocycl. Compd.* **2004**, *40*, 214; a) G. W. Kabalka, A. R. Mereddy, *Tetrahedron Lett.* **2005**, *46*, 6315; b) V. Y. Sosnovskikh, R. A. Irgashev, *Tetrahedron Lett.* **2007**, *48*, 7436; a) A. G. P. R. Figueiredo, A. C. Tomé, A. M. S. Silva, J. A. S. Cavaleiro, *Tetrahedron* **2007**, *63*, 910; a) M. Terzidis, C. A. Tsoleridis, J. Stephanidou-Stephanatou, *Tetrahedron* **2007**, *63*, 7828; a) G. C. Kaspentakis, C. A. Tsoleridis, J. Stephanidou-Stephanatou, *J. Heterocycl. Chem.* **2007**, *44*, 425; a) S. K. Panja, P. Karmakar, J. Chakraborty, T. Ghosh, C. Bandyopadhyay, *Tetrahedron Lett.* **2008**, *49*, 4397; b) O. Prakash, R. Kumar, V. Parkash, *Eur. J. Med. Chem.* **2008**, *43*, 435; a) T. N. M Musthafa, Z. Siddiqui, F. Husain, I. Ahmad, *Med. Chem. Res.* **2011**, *20*, 1473; a) S. D. Diwakar, R. S. Joshi, C. H. Gill, *J. Heterocycl. Chem.* **2011**, *48*, 882.

63 a) S. R. Sarda, M. Y. Pathan, V. V. Paike, P. R. Pachmase, W. N. Jadhav, R. P. Pawar, *Arkivoc* **2006**, *16*, 43; b) A. Lahyani, M. Trabelsi, *Ultrason. Sonochem.* **2016**, 31, 626; c) J. Lee, J. Yu, S. H. Son, J. Heo, T. Kim, J.-Y. An, K.-S. Inna N.-J. Kim, *Org. Biomol. Chem.* **2016**, *14*, 777; d) R. Liu, Y. Zhang, K. Xu, G. Tan, *Synth. Commun.* **2017**, *47*, 1; e) D. Zhai, L. Chen, M. Jia, S. Ma, *Adv. Synth. Catal.* **2018**, *360*, 153; f) Z. Zheng, Y. Wang, M. Xu, L. Kong, M. Wang, Y. Li, *Chem. Commun.* **2018**, *54*, 6192; g) M. Meng, G. Wang, L. Yang, K. Cheng, C. Qi, *Adv. Synth. Catal.* **2018**, *360*, 1218; h) X.-R. Song, R. Li, T. Yang, X. Chen, H. Ding, Q. Xiao, Y.-M. Liang, *Eur. J. Org. Chem.* **2018**, 5548.

en C3. Consultando la bibliografía, sorprende el escaso número de métodos sintéticos para obtener tioflavonas respecto al abanico de posibilidades existente en el caso de flavonas. Este contraste se hace aún más acusado en el caso de las selenoflavonas.

En el caso de las tioflavonas es posible aplicar la condensación de Claisen de manera análoga a las flavonas pero partiendo de *orto*-tioarilcetonas.[64] Tambien se pueden obtener por ciclación de inonas,[65] con cetonas α,β-insaturadas[66] y mediante la condensación entre *orto*-haloarilcetonas y ditioesteres[67] (Esquema II.25).

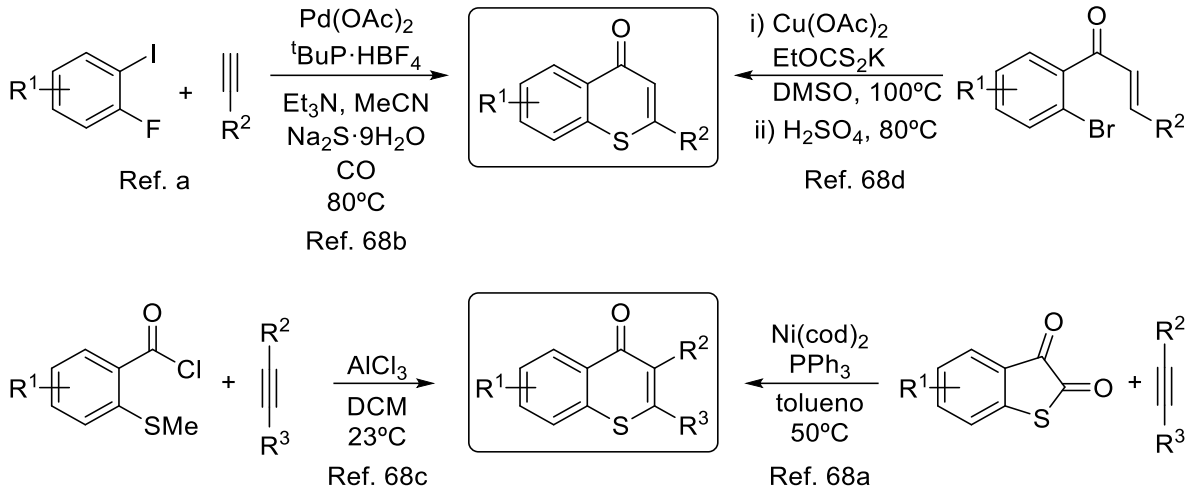


Esquema II.25

Estos métodos son sencillos y dan buenos resultados, pero requieren el uso de bases y ácidos fuertes que limitan su aplicabilidad. Por ello, para evitar o minimizar estos inconvenientes, en los últimos años los métodos catalizados por metales están ganando protagonismo. Permiten condiciones más suaves de

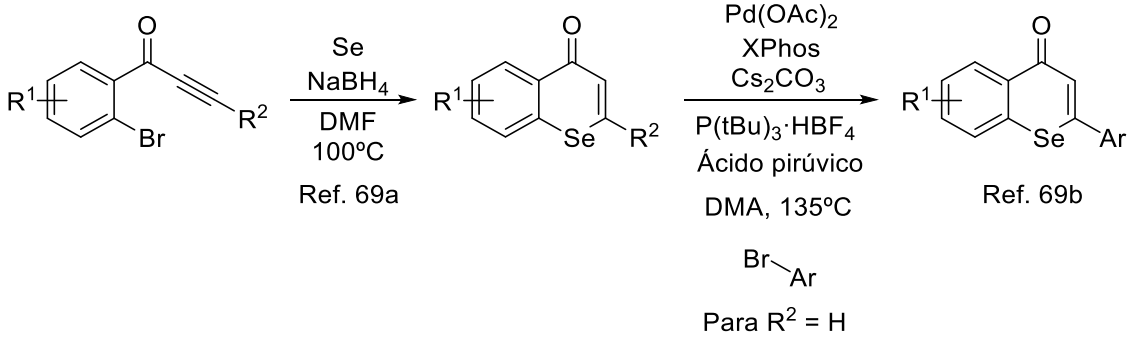
64 J. I. Lee, M. J. Kim, *Bull. Korean Chem. Soc.* **2011**, *32*, 4.
65 J. I. Lee, J. S. Choi, *J. Korean Chem. Soc.* **2015**, *59*, 3.
66 D. Wang, P. Sun, P. Jia, J. Peng, Y. Yue, C. Chen, *Synthesis* **2017**, 49.
67 T. A. J. Vijay, K. N. Nandeesh, G. M. Raghavendra, K. S. Rangappa, K. Mantelingu, *Tetrahedron Lett.* **2013**, *54*, 6533.

reacción y en los casos en los que es necesario el uso de bases o ácidos, estos suelen ser mucho más débiles o se encuentran diluidos. Mientras que el paladio es el metal predominante en la síntesis de flavonas, en el caso de las tioflavonas, se han escogido otros metales para lograr su síntesis en función de los precursores utilizados (Esquema II.26).[68]



Esquema II.26

Consultando la bibliografía existente en cuanto a la síntesis de selenoflavonas, solo encontramos un método para conseguir la formacion del núcleo heterocíclico a partir de *orto*-haloinonas, selenio elemental y borohidruro sódico como agente reductor. También encontramos un protocolo para funcionalizar la posicion C2 catalizado por paladio (Esquema II.27).[69]



Esquema II.27

[68] a) T. Inami, T. Kurahashi, S. Matsubara, *Org. Lett.* **2014**, *16*, 5660; b) C. Shen, A. Spannenberg, X.-F. Wu, *Angew. Chem. Int. Ed.* **2016**, *55*, 5067; c) H. Y. Kim, E. Song, K. Oh, *Org. Lett.* **2017**, *19*, 312; d) S. Sangeetha, G. Sekar, *Org. Lett.* **2019**, *21*, 75.

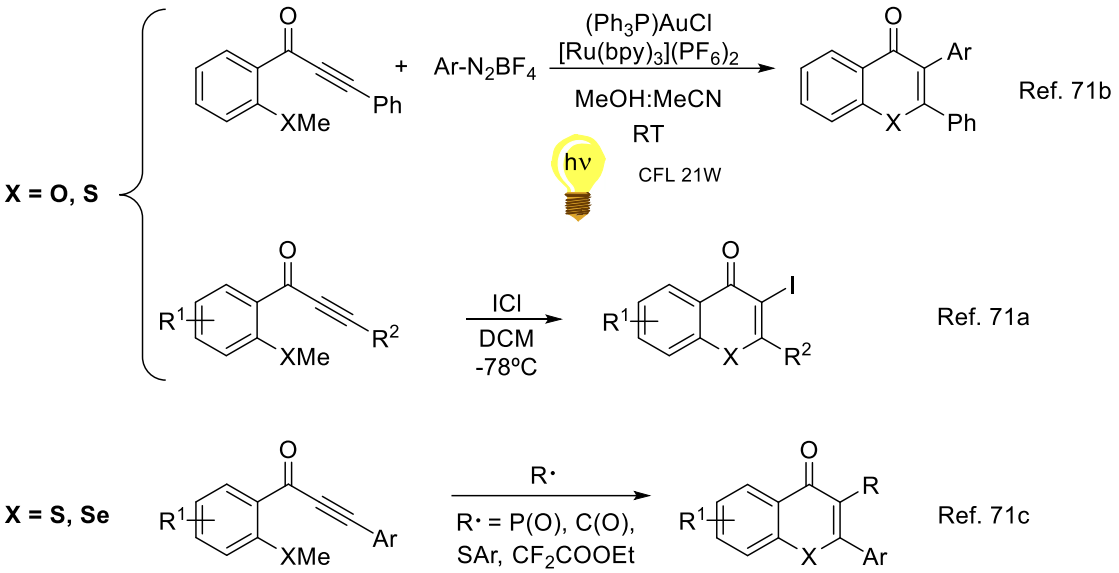
[69] a) H. Sashida, *Synthesis* **1998**, *05*, 745; b) W.-R. Yang, Y.-S. Choi, J.-H. Jeong, *Org. Biomol. Chem.* **2017**, *15*, 3074.

Muy recientemente se ha descrito un método adicional que permite acceder a seleflavonas por una vía radicalaria, este método es el último recogido en el Esquema II.28. La exigua cantidad de protocolos para sintetizar selenoflavonas podemos achacarla a que de toda la familia de flavonas es la que menos interés suscita, principalmente porque el selenio, aunque es un oligoelemento, presenta una alta toxicidad para la mayoría de organismos. Esto ha hecho que este heterociclo haya sido prácticamente ignorado y en consecuencia haya experimentado desinterés por el desarrollo de nuevos métodos sintéticos para su obtención. Sin embargo, en los últimos años han aparecido algunos estudios en los que se demuestra su actividad biológica como protectores neuronales, antioxidantes y antiobesidad.[70]

Por otro lado, después de analizar la mayoría de métodos sintéticos para producir flavonas, tioflavonas y selenoflavonas observamos muy pocos casos en los que un mismo protocolo puede utilizarse para sintetizar diferentes núcleos. De hecho, hasta la fecha solo existen tres métodos[71] y uno de ellos se ha desarrollado en nuestro grupo de trabajo e implica un proceso fotorredox catalizado por oro que permite la formacion de flavonas o tioflavonas mediante ciclación de aril-inonas *orto*-funcionalizadas, con la incorporación de un resto arilo procedente de una sal de diazonio. El grupo de Larock consigue ciclar inonas mediante el uso de cloruro de yodonio para obtener la misma clase de heterociclo. El último método desarrollado recientemente logra la síntesis de tio- y selenoflavonas también a partir de inonas mediante la formación de radicales (Esquema II.28).

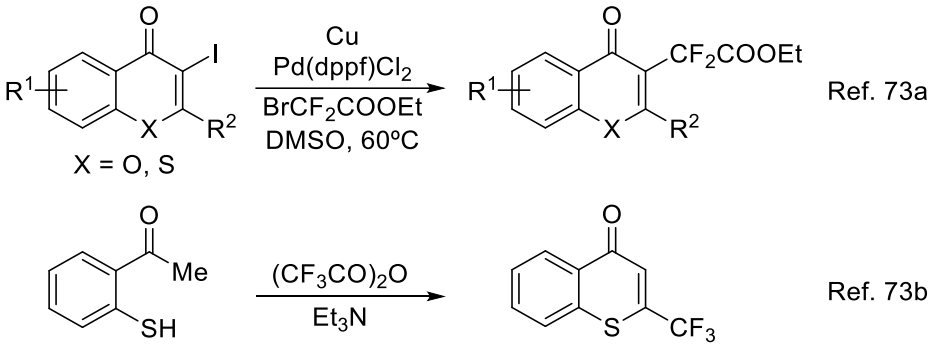
[70] Y. S. Choi, Y. J. Kim, J. Y. Lee, J. Lee, J. H. Jeong, *Heterocycles* **2014**, *89*, 2794.

[71] a) C. Zhou, A. V. Dubrovsky, R. C. Larock, *J. Org. Chem* **2006**, *71*, 4; b) B. Alcaide, P. Almendros, E. Busto, F. Herrera, C. Lázaro-Milla, A. Luna, *Adv. Synth. Catal.* **2017**, *359*, 2640; c) J. Xu, F. Zhang, S. Zhang, L. Zhang, X. Yu, J. Yan, Q. Song, *Org. Lett.* **2019**, *21*, 1112.



Esquema II.28

Junto a la falta de versatilidad o alcance de los procedimientos existentes, otra observación a considerar es la falta de métodos que permitan introducir grupos fluorados en la estructura de manera directa. El flúor es un elemento que ha demostrado ser de particular interés ya que puede mejorar diferentes propiedades de los compuestos sin afectar su actividad biológica.[72] Por ello, resulta sorprendente que en el campo de las flavonas, con un claro protagonismo en el mundo farmacológico, apenas existan métodos para introducir grupos organofluorados en la estructura. Los métodos más destacados de la bibliografía se recogen en el Esquema II.29, junto al último presentado en el Esquema II.28 anterior.[73]



Esquema II.29

[72] La importancia del flúor se tratará en detalle en el siguiente apartado de Antecedentes Generales: II.6 Fluoroalquilaciones en Heterociclos.

[73] a) B. I. Usachev, M. A. Shafeev, V. Ya. Sosnovskikh, *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 3; b) X. Han, Z. Yue, X. Zhang, Q. He, C. Yang, *J. Org. Chem.* **2013**, *78*, 4850.

En 2018, nuestro grupo de trabajo publicó un método que, en las mismas condiciones de reacción, permitía acceder a flavonas, tio- y selenoflavonas indistintamente a partir de inonas, en las que se había introducido previamente el heteroátomo deseado. Además, este método produce simultáneamente la fluoroalquilación de la posicion C3 del núcleo heterocíclico con el resto CH_2CHTf_2. Todo ello en ausencia de catalizadores u otros aditivos o irradiación y a temperatura ambiente. Se trata por tanto de un método novedoso y versátil en unas condiciones inusualmente ventajosas y de interés en el campo de los compuestos organofluorados. Este trabajo forma parte de la presente Tesis y será tratado en detalle en el Capítulo 4 y en su correspondiente apartado dentro de la Discusión General.

II.4.2. Auronas

La aurona es un heterociclo que contiene un anillo de benzofurano con un grupo bencilideno unido en la posición C2 (Figura II.12).

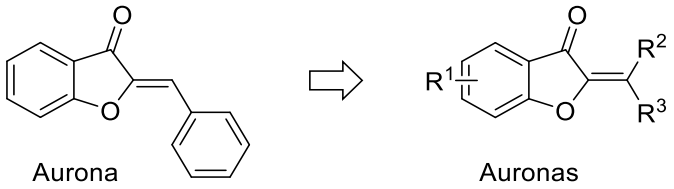


Figura II.12

Es un isómero estructural de las flavonas y al igual que estas una clase de flavonoide. La aurona es el representante más sencillo de la famila de compuestos conocido como auronas. Tales compuestos, junto con las chalconas, dihidrochalconas, flavanonas y dihidroflavonoles, se consideran flavonoides menores como resultado de su abundancia limitada en la naturaleza respecto a otros compuestos de la familia. Sin embargo, las auronas, que también son de origen vegetal, desempeñan papeles cruciales como pigmentos en la coloración de las flores de varias especies de angiospermas, aumentando su atractivo para los polinizadores. De hecho, son responsables de la mayoría de las tonalidades

amarillas, de ahí su nombre, aurona, procedente del latin *aurum*, oro.[74] También se ha identificado su papel como fitoalexinas, compuestos usados por las plantas en sus mecanismos de defensa frente a infecciones microbianas.[75]

Tal vez eclipsadas por las flavonas, no han recibido la atención necesaria, ya que aun siendo conocidas desde mediados del siglo pasado no ha sido hasta principios de este siglo cuando empezaron a levantar interés, debido al descubrimiento de un prometedor espectro de actividades como anticancerígenos, [76] antioxidantes, [77] antiparasitarios, [78] antibacterianos, [79] y antifúngicos.[80] También, han demostrado ser buenos inhibidores de enzimas como la xantina oxidasa[81] (posible tratamiento para la hiperuricemia y gota), la ARN-

[74] a) *Methods in plant biochemistry. Plant phenolics 1.* B. A. Bohm, Academic Press. **1989**; b) B. Boucherle, M. Peuchmaur, A. Boumendjel, R. Haudecoeur, *Phytochemistry* **2017**, *142*, 92; c) G. S. Hassan, H. H. Georgey, R. F. George, E. R. Mohamed, *Bull. Fac. Pharm. Cairo Univ.* **2018**, *56*, 121.

[75] R. K. Dubey, P. Dixit, S. Arya, *IJIRSET* **1987**, *3*, 8141.

[76] a) A. Boumendjel, *Curr. Med. Chem.* **2003**, *10*, 2621; b) S. Okombi, D. Rival, S. Bonnet, A.-M. Mariotte, E. Perrier, A. Boumendjel, *J. Med. Chem.* **2006**, *49*, 329; c) W. Huang, M.-Z. Liu, Y. Li, Y. Tan, G.-F. Yang, *Bioorg. Med. Chem.* **2007**, *15*, 5191; d) H. M. Sim, C. Y. Lee, P. L. Ee, M. L. Go, *Eur J. Pharm. Sci.* **2008**, *35*, 293; e) N. J. Lawrence, D. Rennison, A. T. McGown, J. A. Hadfield, *Bioorg. Med. Chem. Lett.* 2003, 13, 3759; f) H. Cheng, L. Zhang, Y. Liu, S. Chen, H. Cheng, X. Lu, Z. Zheng, G.-C. Zhou, *Eur. J. Med. Chem.* **2010**, *45*, 5950; g) C.-Y. Lee, E.-H. Chew, M.-L. Go, *Eur. J. Med. Chem.* **2010**, *45*, 2957; h) S. Demirayak, L. Yurttas, N. Gundogdu-Karaburun, A.C. Karaburun, I. Kayagil, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 816; i) X. Zheng, H. Wang, Y.-M. Liu, X. Yao, M. Tong, Y.-H. Wang, D.-F. Liao, *J. Heterocyclic Chem.* **2015**, *52*, 296.

[77] a) C. G. Nordstrom, T. Swain, Archiv. *Biochem. Biophys.* **1956**, *60*, 329; b) A. Detsi, M. Majdalani, C. A. Kontogiorgis, D. Hadjipavlou-Litina, P. Kefalas, *Bioorg. Med. Chem.* **2009**, 17, 8073; c) G.S. Hassan, H. H. Georgey, R. F. George, E. R. Mohammed, *Future Med. Chem.* **2018**, *10*, 27.

[78] a) O. Kayser, A.F. Kiderlen, *Tokai J. Exp. Clin. Med.* **1999**, *28*, 423; b) T.T. Huong, N.X. Cuong, H. T. Le, T. T. Quang, V. D. Le, N. H. Nam, N. T. Dat, P. T. Huong, C. N. Diep, P. V. Kiem, C. V. Minh, *J. Asian Nat. Prod. Res.* **2012**, *14*, 923; c) M. Roussaki, S. C. Lima, A.-M. Kypreou, P. Kefalas, A. Cordeiro da Silva, A. Detsi, *Int, J. Med. Chem.* **2012**, 1; d) T. Narsinghani, M. C. Sharma, S. Bhargav, *Med. Chem. Res.* **2013**, *22*, 4059.

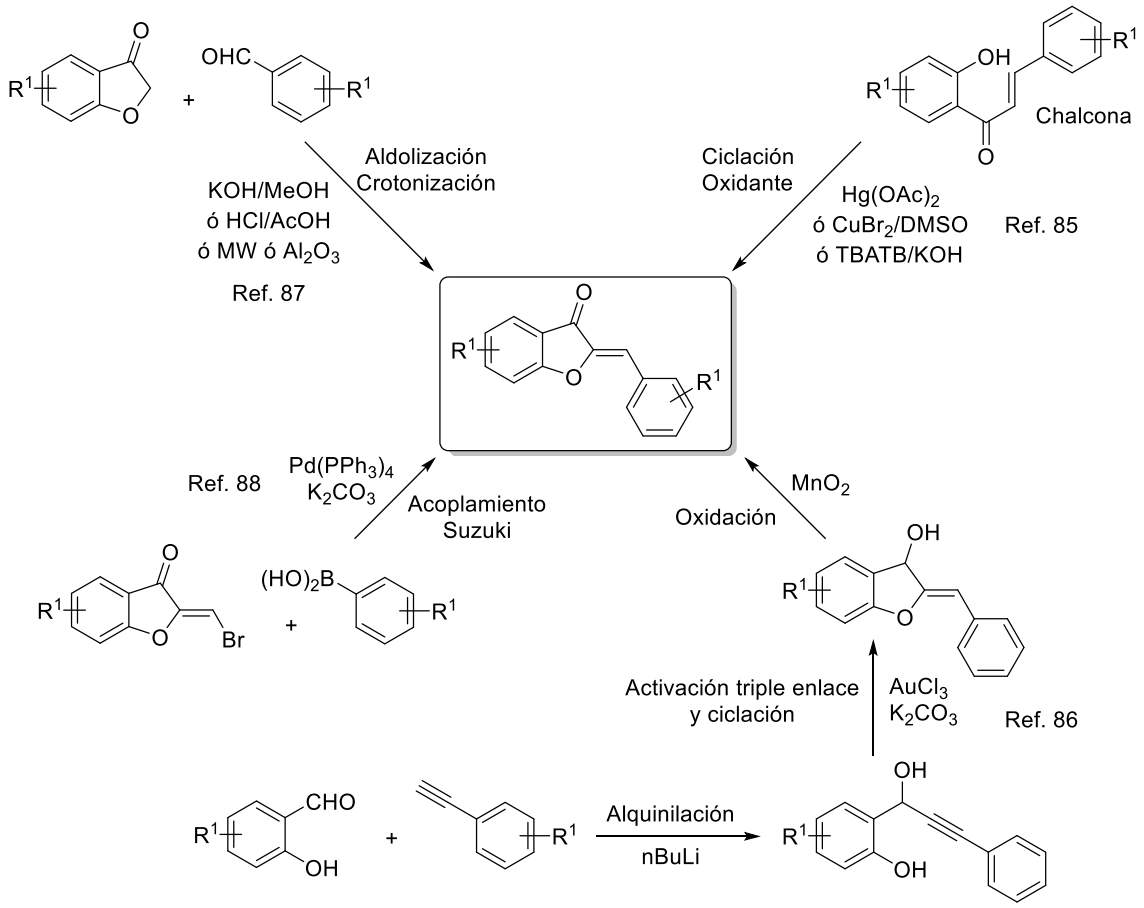
[79] a) F. Souard, S. Okombi, C. Beney, S. Chevalley, A. Valentin, A. Boumendjel, *Bioorg. Med. Chem.* **2010**, *18*, 5724; b) M. P. Carrasco, A. S. Newton, L. Gonçalves, A. Góis, M. Machado, J. Gut, F. Nogueira, T. Hänscheid, R. C. Guedes, D. J. V. A. dos Santos, P. J. Rosenthal, R. Moreira, *Eur. J. Med. Chem.* **2014**, *80*, 523; c) H. Olleik, S. Yahiaoui, B. Roulier, E. Courvoisier-Dezord, J. Perrier, B. Pérès, A. Hijazi, E. Baydoun, J. Raymond, A. Boumendjel, M. Maresca, R. Haudecoeur, *Eur. J. Med. Chem.* **2019**, *165*, 133.

[80] Caleb L. Sutton, Zachary E. Taylor, Mary B. Farone, Scott T. Handy, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 901.

[81] O. V. Muzychka, O. L. Kobzar, A. V. Popova, M. S. Frasinyuk, A. I. Vovk, *Bioorg. Med. Chem.* **2017**, *25*, 3606.

polimerasa del virus de la hepatitis C [82] y acetilcolinesterasa (AChE) para el tratamiento del Alzheimer.[83]

El número de metodologías existentes para sintetizar esta clase de compuestos es menor que en el caso de las flavonas.[84] Algunos de los métodos más comúnmente utilizados se muestran en el Esquema II.30.



Esquema II.30

Una de las estrategias utilizadas consiste en la ciclación oxidante de chalconas, la cual se puede producir en diversas condiciones, utilizando acetato de mercurio (II), nitrato de talio (II), tribromuro de tetrabutilamonio o bromuro de cobre

82 A. Meguellati, A. Ahmed-Belkacem, W. Yi, R. Haudecoeur, M. Crouillère, R. Brillet, J. Pawlotsky, A. Boumendjel, M. Peuchmaur, *Eur. J. Med. Chem.* **2014**, *80*, 579.

83 a) N. Nenadis, M. F. Sigalas, *J. Phys. Chem. A.* **2008**, *112*, 12196; a) R. Sheng, Y. Xu, C. Hu, J. Zhang, X. Lin, J. Li, B. Yang, Q. He, Y. Hu, *Eur. J. Med. Chem.* **2009**, *44*, 7.

84 a) R. Haudecoeur, A. Boumendjel, *Curr. Med. Chem.* **2012**, *19*, 2861; b) A. R. Mahesh, V. Murugan, *European J. Biomed. Pharm. Sci.* **2016**, *3*, 112.

(II).[85] Sin embargo, el uso de metales altamente tóxicos como el mercurio y el talio hace perder atractivo a estas reacciones. Por ello se han desarrollado metodologias que emplean metales menos perjudiciales ambientalmente y en menores cantidades. El oro es un excelente metal π-fílico que interacciona fácilmente con los triples enlaces; por ello es posible conseguir la ciclación de *orto*-hidroxiarilalquinoles utilizando cloruro de oro (I) como catalizador. Con una posterior oxidación de los hidroxi-dihidrofuranos se obtiene el núcleo de aurona.[86] En realidad, el método más utilizado consiste en la condensación aldólica de benzofuran-3-(2*H*)-onas con un aldehído. Esta reacción se puede llevar a cabo en condiciones básicas, ácidas, soportada sobre óxido de aluminio o haciendo uso de un reactor microondas en ausencia de disolventes.[87] La condensación aldólica genera las auronas con buenos rendimientos y con una amplia gama de sustituyentes. Finalmente, pueden aplicarse métodos bien conocidos como el acoplamiento cruzado catalizado por paladio de Suzuki entre una 2-(bromometilen)-benzofuran-3-(2*H*)-ona y un ácido borónico.[88]

En los últimos años se han introducido modificaciones en algunos de estos protocolos para mejorarlos en diferentes aspectos y se han desarrollado algunas metodologías novedosas.[89]

Sin embargo, en la bibliografía solo encontramos dos métodos para la síntesis de un tipo poco común de auronas, las vinil-auronas (Esquema II.31).[90]

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[85] a) H. Sekizaki, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1407; b) K. Thakkar, M. Cushman, *Tetrahedron Lett.* **1994**, 35, 6441; c) K. Thakkar, M. Cushman, *J. Org. Chem.* **1995**, 60, 6499; d) G. Bose, E. Mondal, A. T. Khan, M. J. Bordoloi, *Tetrahedron Lett.* **2001**, 42, 8907; e) N. N. Agrawal, P. A. Soni, *Indian J. Chem.* **2006**, *45B*, 1301.

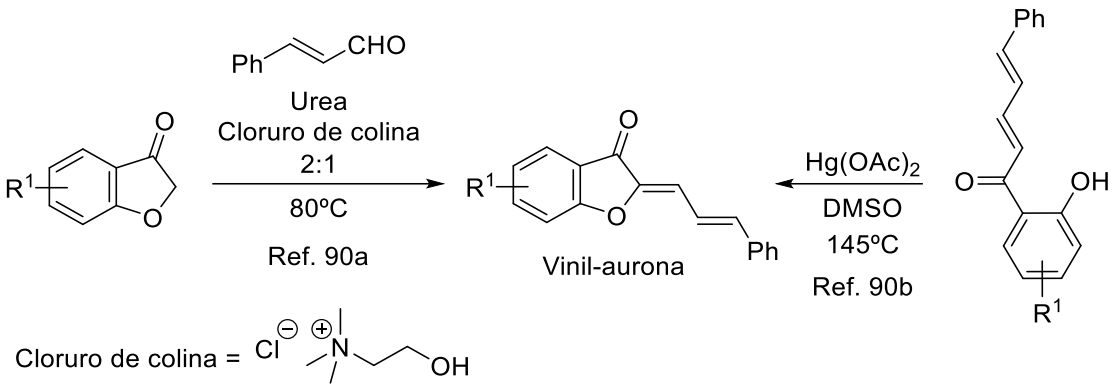
[86] H. Harkat, A. Blanc, J.-M. Weibel, P. Pale, *J. Org. Chem.* **2008**, *73*, 1620.

[87] a) T. A. Geissman, J. B. Harborne, *J. Am. Chem. Soc.* **1955**, *77*, 4622; b) R. S. Varma, M. Varma, *Tetrahedron Lett.* **1992**, *33*, 5937; c) D. Villemin, B. Martin, N. Bar, *Molecules* **1998**, *3*, 88; d) S. Okombi, D. Rival, S. Bonnet, A.-M. Mariotte, E. B. Perrier, *J. Med. Chem.* **2006**, *49*, 329.

[88] G. A. Kraus, V. Gupta, *Org. Lett.* **2010**, 12, 5278.

[89] a) Y. Li, X. Qiang, L. Luo, Y. Li, G. Xiao, Z. Tan, Y. Deng, *Bioorg. Med. Chem.* **2016**, 24, 2342; b) T. Yatabe, X. Jin, N. Mizuno, K. Yamaguchi, *ACS Catal.* **2018**, *8*, 4969; c) J. I. Lee, *Bull. Korean Chem. Soc.* **2018**, *39*, 679; d) M.-Y. Chang, H.-Y. Chen, Y.-L. Tsai, *J. Org. Chem.* **2019**, *84*, 326; e) I. Parveen, N. Ahmed, *Synthesis* **2019**, *51*, 960.

[90] a) I. Hawkins, S. T. Handy, *Tetrahedron* **2013**, *69*, 9200; b) D. Sharmaa, J. K. Makrandi, *J. Hetercyclic Chem.* **2014**, *51*, 1818.



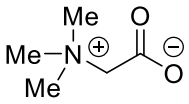
Esquema II.31

En nuestro grupo de trabajo, aunque de manera inesperada, hemos conseguido la síntesis de este tipo de aurona con una reacción que presenta las mismas ventajas que el caso de la obtención de flavonas y tio- y selenoflavonas, aunque en este caso es necesario aplicar calentamiento. Como en el caso de estos compuestos, esta metodología para obtener este particular flavonoide será tratado en el Capítulo 4 y en su apartado correspondiente de la Discusión General.

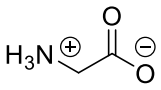
II.5. Carbabetaínas

En química, una betaína es cualquier compuesto químico neutro con un grupo funcional catiónico cargado positivamente no portador de átomos de hidrógeno y con un grupo funcional aniónico cargado negativamente. Ambos grupos no pueden ser adyacentes uno respecto a otro, es decir, no puede existir un enlace directo entre ellos. Una betaína puede considerarse un tipo de zwitterión. Estos últimos presentan en disolución algún tipo de equilibrio que produce la transferencia intramolecular de grupos o átomos para originar las cargas formales positivas y negativas. En el caso de las betaínas no se producen estas transferencias o de producirse son intermoleculares.

Históricamente, el término betaína estaba reservado solo para la trimetilglicina, surgido del nombre científico de la planta de la remolacha, de la que se extrajo y aisló por primera vez este compuesto, *Beta vulgaris*.[91] Con el tiempo se extendió el uso del término betaína para denominar al resto de moléculas con las características comentadas anteriormente. La trimetilglicina es neutra, pero presenta un grupo catiónico en la amina cuaternaria y un grupo aniónico en el carboxilato (Figura II.13).



Betaína
(*Trimetilglicina o betaína de glicina*)



Glicina
(Forma zwitteriónica, pH = 6)

Figura II.13

Los aminoácidos que forman parte de todos los seres vivos, como la propia glicina, no pueden considerarse betaínas cuando están en su forma zwitteriónica, pues el grupo catiónico está unido a átomos de hidrógeno y las cargas parciales se forman por transferencia del protón carboxílico al grupo amino (Figura II.13).

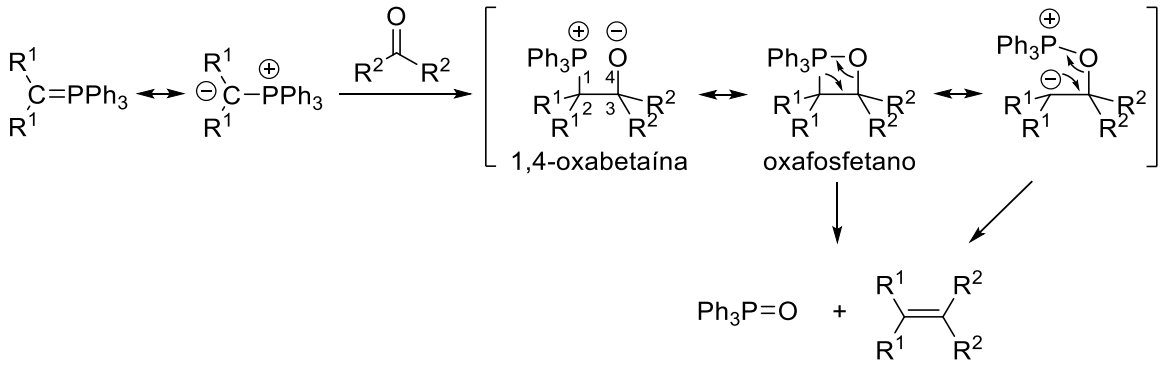
En cualquier caso, el uso estricto de las denominaciones betaína y zwitterión se ha perdido con el tiempo y en general se utilizan ambas palabras indistintamente para definir a aquellas moléculas neutras que presentan grupos con cargas formales

[91] *Organic Chemistry, the Name Game: Modern Coined Terms and Their Origins*. A. Nickon, E. F. Silversmith, Pergamon Press, Oxford, Inglaterra, **1987**.

parciales no enlazados directamente.[92] Un ejemplo claro de este hecho lo tenemos en los propios zwitteriones de Koshar presentados al principio de los Antecedentes Generales, pues la denominación más purista y correcta seria betaínas de Koshar.

En los sistemas biológicos, muchas betaínas de origen natural sirven como osmolitos orgánicos, sustancias sintetizadas o extraídas del medio ambiente por las células para la protección contra el estrés osmótico, la sequía, la alta salinidad o la alta temperatura.[93] La acumulación intracelular de betaínas, sin perturbar la función enzimática, la estructura de las proteínas y la integridad de la membrana, permite la retención de agua en las células, protegiendo así de los efectos de la deshidratación.

En el campo de la Química Orgánica encontramos betaínas en las que la carga formal positiva esta soportada sobre un átomo de fósforo, las denominadas betaínas de fósforo o fosfobetaínas. Son una clase importante de compuestos por su estructura, propiedades, y reactividad.[94] El ejemplo más conocido lo encontramos en la reacción de Wittig[95] (Esquema II.32).



Esquema II.32

En los intermedios de reacción se postula la formación de una 1,4-oxabetaína. Después de tantos años desde el descubrimiento realizado por Wittig, los intermedios betaínicos propuestos siguen siendo objeto de fuerte discusión ya que

92 *Compendium of Chemical Terminology*, 2ª ed. IUPAC. ("Gold Book"). A. D. McNaught, A. Wilkinson. Blackwell Scientific Publications, Oxford, Inglaterra, **1997**.

93 a) *The Physiology and Biochemistry of Drought Resistance in Plants*, L.G. Paleg, D. Aspinall, Academic Press, Sídney, Australia, **1981**; b) M. Nomura, Y. Muramoto, S. Yasuda, T. Takabe, S. Kishitani, *Euphytica* **1995**, *83*, 247; c) M. K. Chattopadhyay *Resonance* **2002**, *7*, 59.

94 a) *A Guide to Organophosphorus Chemistry*, L. D. Quin, Wiley, Nueva York, EEUU, **2000**; b) N. N. Zemlyansky, I. V. Borisova, Y. A. Ustynyuk, *Adv. Organomet. Chem.* **2003**, *49*, 35.

95 G. Wittig, A. Haag, *Chem. Ber.* **1963**, *96*, 1535.

experimentalmente sólo se ha podido detectar por RMN la formación de los oxafosfetanos cíclicos de cuatro miembros.[96] En contraste, sí que se ha conseguido sintetizar los equivalentes de azufre, pero ello se explica porque los enlaces P−S son termodinámicamente más débiles que los P−O, lo que favorece la formación de 1,4-tiobetaínas en detrimento de los tiofosfetanos.[94] Estos resultados experimentales son los responsables de las dudas existentes en torno a los intermedios de la reacción de Wittig.

Los intentos por sintetizar 1,4-oxabetaínas libres para su estudio han fracasado debido a su alta inestabilidad.[97] Lo más cerca de conseguirlo y la mayor parte del conocimiento que se tiene de ellas es gracias a Ionkin y colaboradores,[98] que consiguieron sintetizar y cristalizar, en forma de dímero conectado por un enlace de hidrógeno, la molécula mostrada en la Figura II.14.

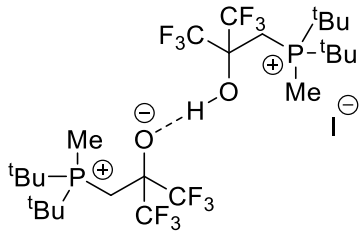


Figura II.14

Directamente relacionadas con las fosfo-oxabetaínas se encuentran las 1,3- y 1,4-fosfocarbabetaínas. La diferencia principal con las primeras se encuentra en que las carbabetaínas poseen la carga formal negativa localizada sobre un carbono (carbanión) y no sobre un átomo de oxígeno. Tampoco encontramos en la bibliografía ejemplos claros de esta clase de carbabetaínas. En la Figura II.15, se muestran dos ejemplos de estructuras equivalentes que se han sintetizado y aislado.[99]

[96] P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, *42*, 6670.

[97] a) M. Schlosser, K. F. Christmann, *Justus Liebigs Ann. Chem.* **1967**, *708*, 1; b) E. Vedejs, G. P. Meier, K. A. J. Snoble, *J. Am. Chem. Soc.* **1981**, *103*, 2823.

[98] A. S. Ionkin, W. J. Marshall, B. M. Fish, M. F. Schiffhauer, F. Davidson, *J. Am. Chem. Soc.* **2007**, *129*, 9210.

[99] a) F. Ramirez, J. F. Pilot, C. P. Smith, *Tetrahedron* **1968**, *24*, 3735; b) F. Ramirez, J. F. Pilot, O. P. Madan, C. P. Smith, *J. Am. Chem. Soc.* **1968**, *90*, 1275; c) E. E. Schweizer, C. M. Kopay, *J. Org. Chem.* **1971**, *36*, 1489; d) X.-F. Zhu, C. E. Henry, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 6722.

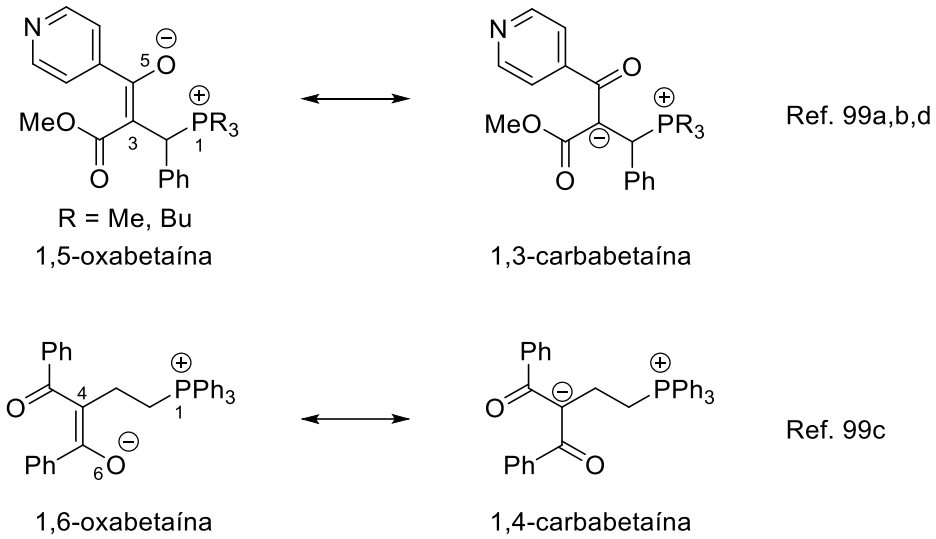
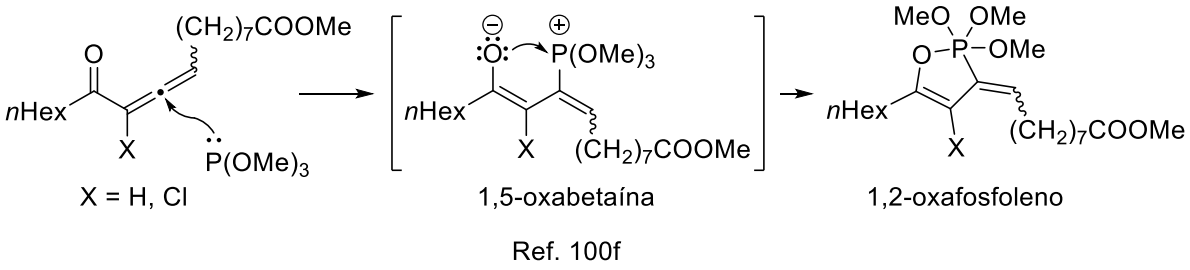


Figura II.15

Sin embargo, en ambos casos la "resonancia ceto-enolica" contribuye más a la forma enólica que a la forma ceto en la que se encuentran las 1,3- y 1,4-carbabetaínas. Por tanto, estas moléculas no son los ejemplos más adecuados para realizar un estudio de fosfocarbabetaínas ya que están más cerca de comportarse como 1,5- o 1,6-oxabetaínas, respectivamente. Además, en el caso de las 1,5-oxabetaínas, son generalmente inestables porque tienen tendencia a evolucionar hacia el cierre de anillo mediante la formación de un enlace P−O, originando los ciclos de cinco miembros denominados 1,2-oxafosfolenos (Esquema II.33).[100]

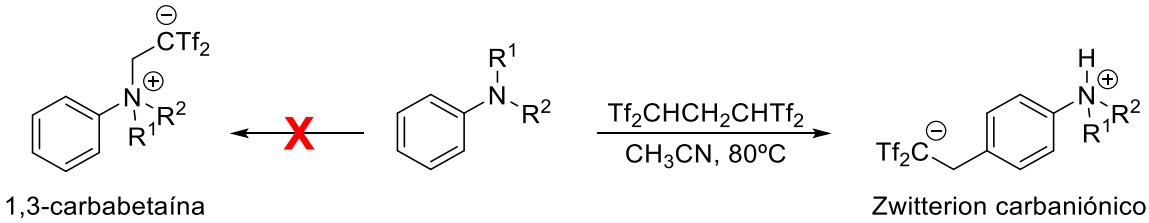


Esquema II.33

[100] a) F. Ramirez, O. P. Madan, S. R. Heller, *J. Am. Chem. Soc.* **1965**, *87*, 731; b) D. Gorenstein, F. H. Westheimer, *J. Am. Chem. Soc.* **1970**, *92*, 634; c) G. Buono, J. R. Llinas, *J. Am. Chem. Soc.* **1981**, *103*, 4532; d) C. K. McClure, K.-Y. Jung, *J. Org. Chem.* **1991**, *56*, 867; e) C. K. McClure, P. K. Mishra, C. W. Grote, *J. Org. Chem*. **1997**, *62*, 2437; f) S. Fermeier, M. M. L. Lau, M. S. F. Lie Ken Jie, A. Letzen, J. O. Metzger, *Eur. J. Org. Chem*. **2003**, 4874.

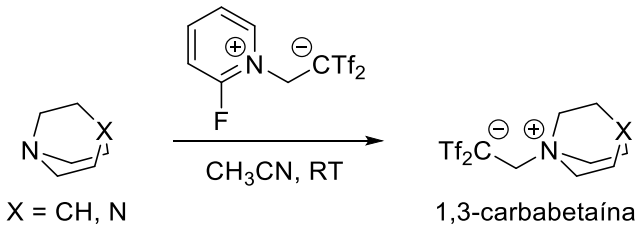
Por tanto, en este campo se hace necesario el desarrollo de metodologías que permitan sintetizar, aislar y caracterizar fosfocarbabetaínas estables.

El grupo de Yanai intentó la formación de carbabetaínas de sales cuaternarias de amonio a partir de aminas terciarias aromáticas y la molécula $Tf_2C{=}CH_2$ generada por el método retro-Michael, pues en ese momento aún no se había desarrollado el estudio sobre los zwitteriones de Koshar. Sorprendentemente, no consiguieron su objetivo principal y en su lugar se produjo una alquilación de la posición *para* del anillo bencénico con el resto aniónico y la protonación de la amina como contraión catiónico, originando el zwitterión carbaniónico mostrado en el Esquema II.34.



Esquema II.34

Tras el re-descubrimiento y estudio de los zwitteriones de Koshar,[7a] que por sí mismos ya son 1,3-carbabetaínas, y tras el desarrollo del zwitterión derivado de la 2-fluoropiridina, Yanai fue capaz de obtener otras 1,3-carbabetaínas a partir de aminas terciarias (Esquema II.35).[7b]



Esquema II.35

El siguiente objetivo era extrapolar esta metodología a fosfinas, equivalentes químicos de las aminas, para obtener las deseadas 1,3-fosfocarbabetaínas así como 1,4-fosfocarbabetaínas a partir de iluros de fósforo. Nuestro grupo de trabajo en colaboración con Yanai, fue capaz de sintetizar dichas betaínas estables, lo que permitió realizar una rigurosa determinación estructural por diferentes técnicas y un estudio de su estructura y propiedades orbitalarias mediante el uso de cálculos computacionales. La publicación fruto de este trabajo es la base del Capítulo 6 y de su correspondiente apartado en la Discusión General de la presente Tesis.

II.6. Fluoroalquilación en heterociclos

La química de compuestos organofluorados es casi tan antigua como la Química Orgánica. En 1835, Dumas preparó fluorometano, el primer compuesto orgánico con flúor, mediante la reacción de fluoruro de potasio con sulfato de dimetilo. Por lo tanto, la química de los organofluorados es solo siete años más joven que la Química Orgánica, que comenzó su historia a partir de la síntesis de urea realizada por Wöhler en 1828. Durante más de un siglo, el estudio de la química de los derivados organofluorados apenas existió. Tal vez el impulso más importante fue debido al desarrollo de armas químicas después de la Segunda Guerra Mundial. Tras esta época, los nuevos reactivos conseguidos para producir fluoraciones intensificaron el desarrollo de este campo dentro de la Química Orgánica, iniciando su progresivo crecimiento.[101]

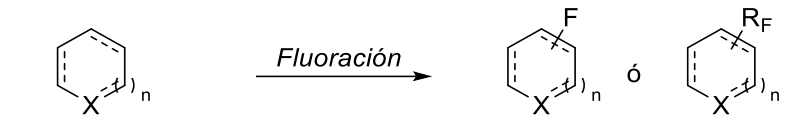
Hoy en día, la introducción de flúor es una herramienta de uso común en Química Médica (fármacos), Agroquímica (agentes de protección de cultivos) y Química de Materiales (teflón).[102] La presencia de flúor puede producir cambios sustanciales de las propiedades biológicas y fisicoquímicas de los compuestos orgánicos, como por ejemplo, la fuerza de enlace, la lipofilia, la biodisponibilidad,

[101] a) *Fluorine in Heterocyclic Chemistry Volume 1, 5-Membered Heterocycles and Macrocycles*, V. Nenajdenko, Springer, Suiza, **2014**; b) *Fluorine in Heterocyclic Chemistry Volume 2, 6-Membered Heterocycles*, V. Nenajdenko, Springer, Suiza, **2014**.

[102] a) *Recent Developments in Fluorine-Containing Agrochemicals. In Organofluorine Chemistry: Principles and Commercial Applications*, D. Cartwright, R. E. Banks, B. E. Smart, J. C. Tatlow, Springer, Boston, EEUU, **1994**; b) *Organofluorine Compounds: Chemistry and Applications*, T. Hiyama, Springer, Nueva York, EEUU, **2000**; c) *Modern Fluoroorganic Chemistry, Synthesis, Reactivity and Applications*, P. Kirsch, Wiley-VCH, Weinheim, Alemania, **2004**; d) P. Jeschke, *ChemBioChem* **2004**, *5*, 571; e) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; f) *Fluorine-Containing Agrochemicals: An Overview of Recent Developments. In Advances in Fluorine Science*, G. Theodoridis, T. Alain, Elsevier, Amsterdam, Holanda, **2006**; g) *Bioorganic and Medicinal Chemistry of Fluorine*, J. P. Bégué, D. Bonnet-Delpon, Wiley-VCH, Weinheim, Alemania, **2008**; h) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; i) *Fluorine in Medicinal Chemistry and Chemical Biology*, I. Ojima, Wiley-Blackwell, Chichester, Inglaterra, **2009**; j) *Agricultural Products Based on Fluorinated Heterocyclic Compounds. In Fluorinated Heterocyclic Compounds*, W. Hong, John Wiley & Sons, Hoboken, EEUU, **2009**; k) P. Jeschke, *Pest Manag. Sci.* **2010**, *66*, 10; a) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071; l) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*, V. Gouverneur, K. Muller, Imperial College Press, London, Inglaterra, **2012**; m) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16; n) G. Landelle, A. Panossian, F. R. Leroux, *Curr. Top. Med. Chem.* **2014**, *14*, 941; o) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422.

aspectos conformacionales, el potencial electrostático, el momento dipolar, el pKa, etc., así como las propiedades farmacocinéticas, como la distribución tisular, la tasa de metabolismo y propiedades farmacológicas, como la farmacodinámica y la toxicología.

Por otro lado, los heterociclos representan uno de los grupos más grandes de compuestos orgánicos y desempeñan un papel importante en todos los aspectos de la química básica y aplicada. Como el resto de compuestos organofluorados, el subgrupo de los heterociclos fluorados inició su desarrollo intenso tras la Segunda Guerra Mundial.[103] Se consideran heterociclos fluorados aquellos que presentan en su anillo la sustitución de un protón por un átomo de flúor o bien aquellos que incorporan un grupo funcional fluorado. Además, pueden ser aromáticos o no aromáticos (Esquema II.36).

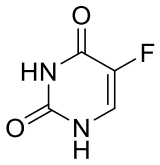


Heterociclos
n = -3,-2,-1,0,1,...
X = O, S, Se, Te, N, P...

Heterociclos fluorados

Esquema II.36

El primer heterociclo fluorado con aplicaciones prácticas fue el 5-fluorouracilo, desarrollado por Heidelberger en 1957 y comercializado en 1962 por la farmacéutica Hoffmann-La Roche.[104] Este investigador demostró que este heterociclo modificado funciona como agente antineoplásico y es un antimetabolito del uracilo natural, convirtiéndose en la primera droga sintética fluorada y uno de los primeros fármacos usados en oncología (Figura II.16).



5-fluorouracilo (5-FU)

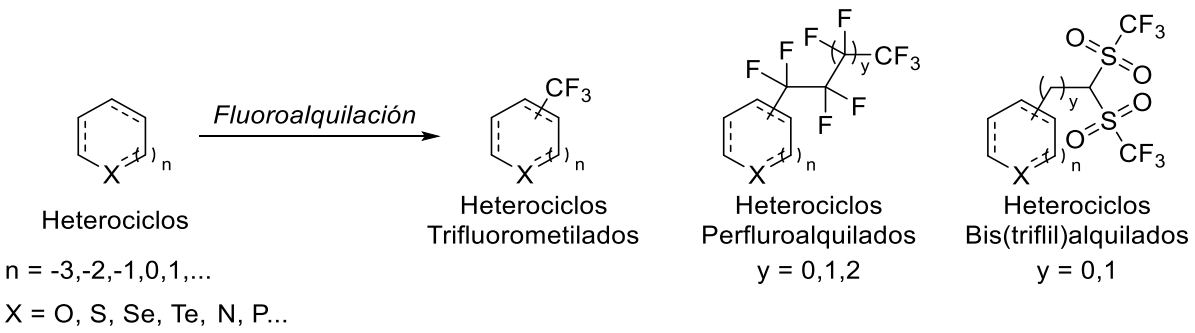
[103] *Fluorinated Heterocyclic Compounds*, V. A. Petrov, John Wiley & Sons, Hoboken, New Jersey, EEUU, **2009**.

[104] C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, J. Scheiner, *Nature* **1957**, *179*, 663.

Figura II.16

En consecuencia, en las últimas décadas, la atractiva gama de aplicaciones que tienen los heterociclos junto con las ventajas que puede aportar la incorporación de flúor, ha hecho que se dedique una atención cada vez mayor al desarrollo de nuevos y más eficientes métodos para la introducción de sustituyentes fluorados en sus anillos. Sin embargo, la diversidad, la complejidad y el comportamiento único de estos compuestos cíclicos, hace difícil encontrar métodos generales y selectivos para introducir este halógeno en sus estructuras.[105]

En esta Memoria nos hemos centrado en la fluoroalquilación de heterociclos ricos en electrones. Los restos alquilfluorados más comunes son el trifluorometilo y cadenas cortas lineales de perfluoroalquilo, tanto en sustratos aromáticos como heteroaromáticos (Esquema II.37).



Esquema II.37

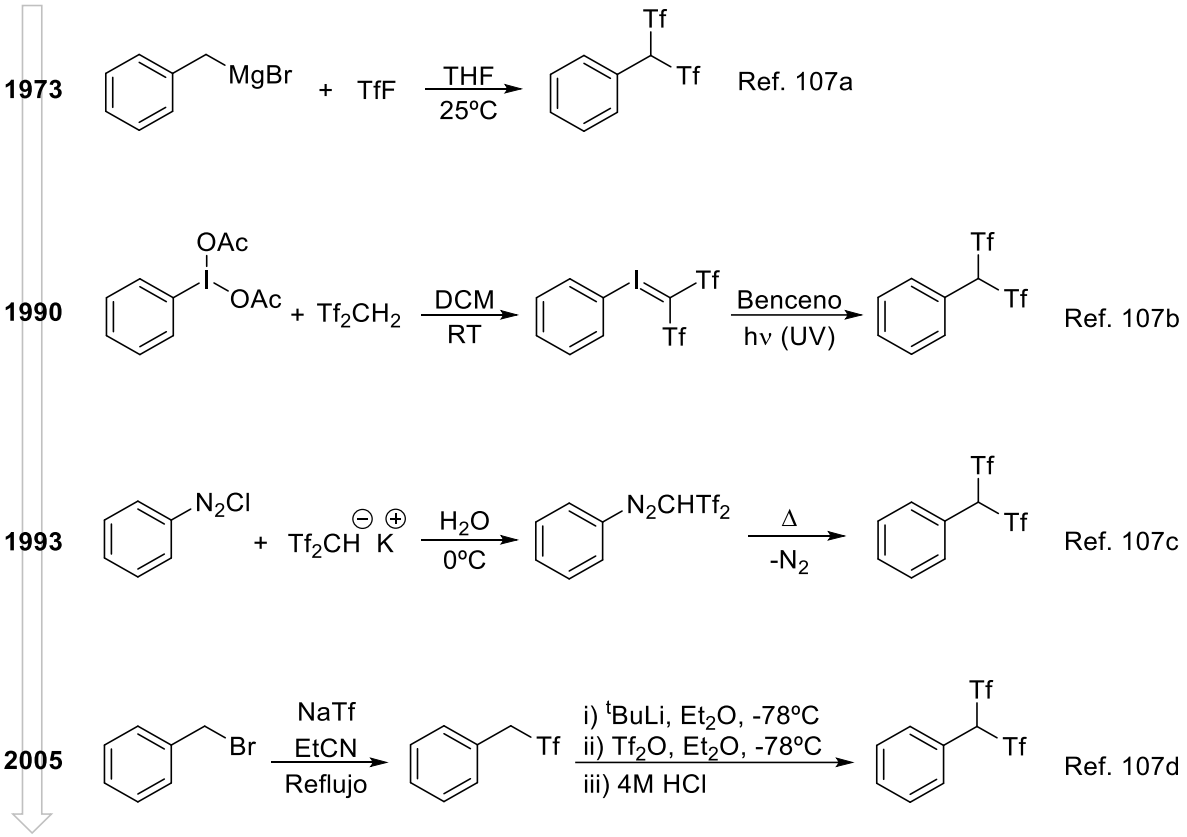
La química para introducir estos sustituyentes $-CF_3$ y $-(CF_2)_yCF_3$ se ha revitalizado en la última década, como demuestra el gran volumen de artículos publicados.[106] Sin embargo, otros grupos alquilfluorados han recibido poca atención;

[105] a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475; b) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679; c) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; d) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683; e) C. Alonso, E. Martínez de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847.

[106] Pequeña muestra representativa de algunos artículos seleccionados de los últimos diez años: a) R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima, M. Sodeoka, *Tetrahedron Lett.* **2010**, 51, 5947; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, 473, 470; c) *Eur. J. Org. Chem.* **2012**, *2012*, 6679; d) F. O'Hara, R.D. Baxter, A.G. O'Brien, M.R. Collins, J.A. Dixon, T. Fujiwara, Y. Ishihara, P.S. Baran, *Nat. Protoc.* **2013**, *8*, 1042; d) G. Danoun, B. Bayermagnai, M. F. Grünberg, C. Matheis, E. Risto, L. J. Gooßen, *Synthesis*, **2014**, *46*, 2283; e) J. Zheng, J.-H. Lin, X.-Y. Deng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 532; f) R. C. Simon, E. Busto, N. Richter, V. Resch, K. N. Houk, W. Kroutil, *Nat. Commun.* **2016**, *7*, 13323; g) J. Dong, S. Xin, Y. Wang, L. Pan, Q. Liu, *Chem. Commun*. **2017**, *53*, 1668; h) T. Shirai, M. Kanai, Y. Kuninobu, *Org. Lett.* **2018**, *20*,

especialmente aquellos que introducen el flúor en la cadena en forma de grupos trifluorometanosulfonilo (Esquema II.37).

Examinando la bibliografía, encontramos que los primeros procedimientos descritos para conseguir anillos aromáticos fluorosulfonilalquilados se desarrollaron entre finales del siglo XX y principios del XXI (Esquema II.38).[107]



Esquema II.38

El primer ejemplo de introducción de este grupo en un anillo aromático lo publica Koshar en 1973. Este método es experimentalmente complejo, ya que requiere floruro de triflilo (TfF), el cual es un gas no comercial, siendo necesaria su generación *in situ*, no exenta de riesgos. Casi veinte años más tarde, Zhu y col. desarrollan un nuevo método en dos etapas, la primera genera el fenilyodonio de bis(triflil)metano que se transforma fotoquimicamente en una segunda etapa con luz

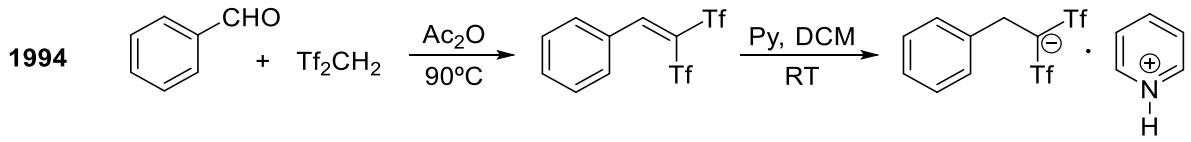
1593; i) R. Wanga, J. Wang, Q. Tang, X. Zhao, J. Wang, Y. Leng, Y. Wua, J. Chang, Y. Wua, Z. Zhang, S. Wang, *Tetrahedron Lett.* **2019**, *60*, 586.

107 a) R. J. Koshar, R. A. Mitsch, *J. Org. Chem.* **1973**, *38*, 3358; b) S.-Z. Zhu, Q.-Y. Chen, *J. Chem. Soc.*, *Chem. Commun.* **1990**, 0, 1459; c) S.-Z. Zhu, *J. Fluor. Chem.* **1993**, *64*, 47; d) A. Hasegawa, T. Ishikawa, K. Ishihara, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1401.

ultravioleta. Años más tarde, este mismo investigador, publica una ruta alternativa mediante la extrusión térmica de nitrógeno de la sal de fenildiazonio de bis(triflil)metano. Finalmente, a principios del siglo XXI, el grupo de Yamamoto, desarrolló otro método en dos etapas a partir de haluros de bencilo mediante la introducción secuencial de dos grupos triflilo.

Si bien estos métodos consiguen introducir la funcionalidad $CHTf_2$, no podemos considerarlos métodos de alquilación directa de arilos, pues se basan en la transformación de un grupo funcional ya presente en la molécula de partida. Sin embargo, la obtención de estos compuestos fue útil para estudiar sus propiedades y potenciales aplicaciones que aporta la introducción del grupo funcional bis(triflil)metilo. Este grupo posee una acidez elevada, por lo que muchos compuestos portadores de esta funcionalidad se han utilizado como catalizadores ácidos en otras reacciones.[108]

Coetáneo a los trabajos anteriores, Zhu en el año 1994,[109] consigue la bis(triflil)etilación de arenos introduciendo el grupo CH_2CHTf_2; pero como en los casos anteriores lo consigue por transformación de grupos funcionales y no por alquilación directa del anillo aromático. (Esquema II.39).



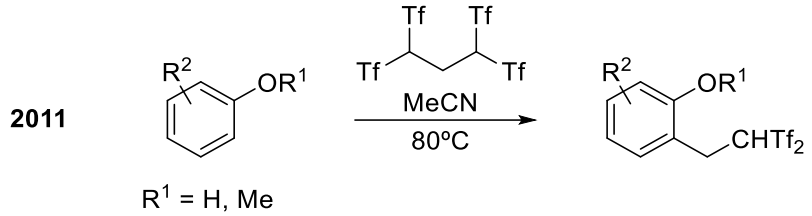
Esquema II.39

No fue hasta el año 2011 cuando el grupo de Yanai desarrolló un método para conseguir la C-H alquilación directa y selectiva de anillos fenólicos o metoxibencenos

[108] a) K. Ishihara, A. Hasegawa, H. Yamamoto, *Angew. Angew. Chem. Int. Ed.* **2001**, *40*, 4077; b) K. Ishihara, A. Hasegawa, H. Yamamoto, *Synlett* **2002**, 1296; c) K. Ishihara, A. Hasegawa, H. Yamamoto, Synlett **2002**, 1299; d) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175; e) H. Yanai, T. Taguchi, *Chem. Commun.* **2012**, *48*, 8967; f) H. Yanai, N. Ishii, T. Matsumoto, T. Taguchi, *Asian J. Org. Chem.* **2013**, *2*, 989; g) H. Yanai, N. Ishii, T. Matsumoto, *Chem. Commun.* **2016**, *52*, 7974; h) H. Yanai, O. Kobayashi, K. Takada, T. Isono, T. Satohb, T. Matsumoto, *Chem. Commun.* **2016**, *52*, 3280.
Para el uso de $Tf_2CHCH_2CHTf_2$ como catalizador ácido, consultar: i) A. Takahashi, H. Yanai, T. Taguchi, *Chem. Commun.* **2008**, 2385; j) H. Yanai, A. Takahashi, T. Taguchi, *Chem. Commun.* **2010**, *46*, 8728; k) H. Yanai, Y. Yoshino, A. Takahashi, T. Taguchi, *J. Org. Chem.* **2010**, *75*, 5375; l) A. Takahashi, H. Yanai, M. Zhang, T. Sonoda, M. Mishima, T. Taguchi, *J. Org. Chem.* **2010**, *75*, 1259.

[109] S.-Z. Zhu, *Synthesis* **1994**, *3*, 261.

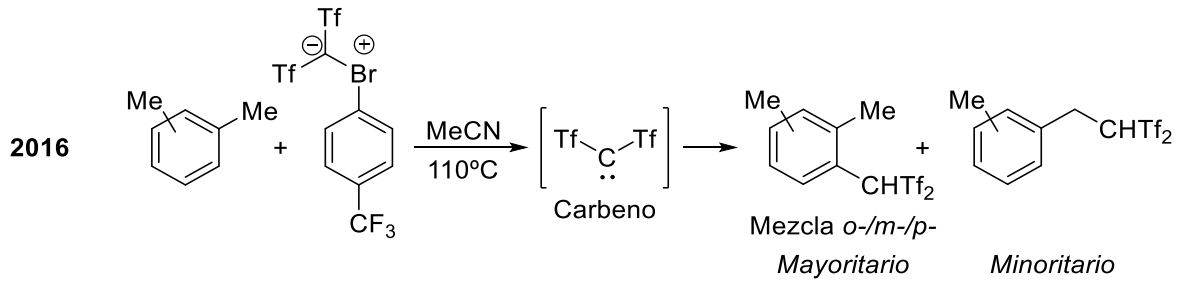
sustituidos en sus posiciones *orto*-activadas.[4a] Para ello utilizó la molécula altamente polarizada $Tf_2C{=}CH_2$ generada *in situ* por el método retro-Michael (Esquema II.40).



Esquema II.40

En este caso la molécula de $Tf_2C{=}CH_2$ no se comporta como un 1,2-dipolo para dar cicloadiciones formales, sino como un aceptor Michael, produciendo la S_EAr.

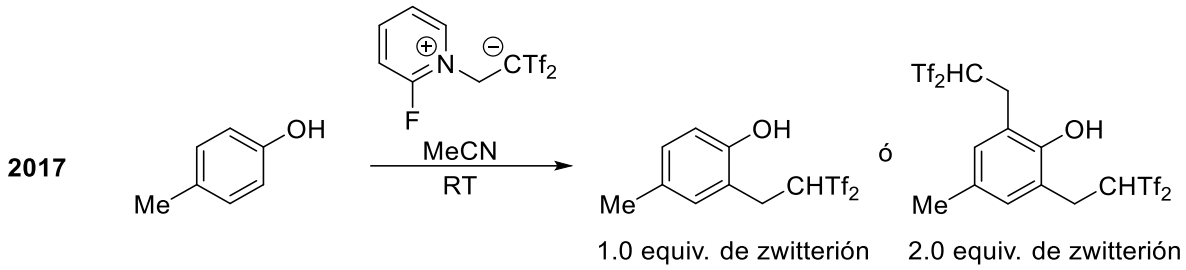
Unos años después se publicó el último método conocido hasta la fecha para lograr la fluoroalquilación directa de arilos. En este caso, mediante la formación *in situ* de carbenos singlete bis(triflil)metil sustituidos.[110] Sin embargo, aunque los rendimientos son buenos el método resulta poco efectivo por su baja selectividad, quedando restringido su uso a sustratos concretos que si presentan buenos resultados (Esquema II.41).



Esquema II.41

Tras el desarrollo del zwitterión derivado de la 2-fluoropiridina, Yanai demostró que también era posible utilizar esta fuente latente de $Tf_2C{=}CH_2$ para producir la fluorosulfonilalquilación de los fenoles que había preparado anteriormente por el método retro-Michael, pero en condiciones mucho más suaves y en consecuencia más selectivas (Esquema II.42).[7b]

[110] K. Miyamoto, S. Iwasaki, R. Doi, T. Ota, Y. Kawano, J. Yamashita, Y. Sakai, N. Tada, M. Ochiai, S. Hayashi, W. Nakanishi, M. Uchiyama, *J. Org. Chem.* **2016**, *81*, 3188.



Esquema II.42

Tras una búsqueda exhaustiva en la bibliografía, no encontramos ningún heterociclo que se haya funcionalizado con el resto $CHTf_2$ o CH_2CHTf_2. Además, al observar la avidez de la molécula $Tf_2C{=}CH_2$ por posiciones CH nucleófilas, pensamos que heterociclos π-excedentes, así como aquellos no aromáticos pero con posiciones especialmente activadas, deberían ser excelentes sustratos para conseguir sus versiones fluorosulfonilalquiladas. Esta premisa nos llevó a colaborar junto al grupo de trabajo de Yanai para desarrollar la metodología que ha permitido, por primera vez, obtener selectivamente heterociclos funcionalizados con el grupo CH_2CHTf_2. En este trabajo se fundamenta el Capítulo 7 y su correspondiente apartado en la Discusión General, donde será tratado en detalle.

II.7. 1,2,3-Triazoles

Los 1,2,3-triazoles son compuestos heterocíclicos aromáticos de cinco eslabones que contienen tres átomos de nitrógeno contiguos. Cuando el núcleo de 1,2,3-triazol no se encuentra sustituido en el nitrógeno puede presentarse como 1*H*- o como 2*H*-triazol, ya que estas dos formas tautoméricas están en equilibrio en disolución (Figura II).[111]

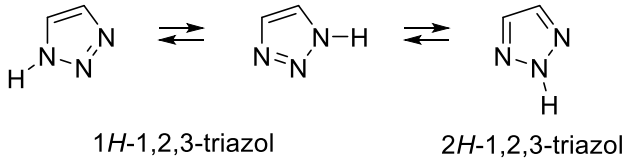


Figura II.17

Sin embargo, normalmente, el nitrógeno de la posición uno se encuentra enlazado a un sustituyente, lo que provoca que el equilibro se encuentre extremadamente desplazado hacia la forma tautómera 1*H*, haciendo que la proporción de la forma 2*H* sea despreciable.

Los 1,2,3-triazoles son importantes en diversas áreas de investigación, fundamentalmente en química médica, agroquímica y ciencias de materiales. Aunque los 1,2,3-triazoles no están presentes en productos naturales sus particulares características los han convertido en moléculas importantes en farmacología.[112] Son muy resistentes, tanto a la reducción como a la oxidación, así como a la hidrólisis en condiciones ácidas o básicas, debido principalmente a su aromaticidad, lo que les confiere una alta estabilidad. Tienen un momento dipolar elevado y forman enlaces de hidrógeno con facilidad. También pueden presentar interacciones dipolo-dipolo e interacciones π-π (*π-stacking*). Estas propiedades hacen que interaccionen fácilmente con las dianas biológicas, lo que les otorga una amplia gama de bioactividades.[113] Se ha demostrado su capacidad para actuar

[111] F. Tomas, J.-L. M. Abboud, J. Laynez, R. Notario, L. Santos, S.O. Nilsson, J. Catalán, R.M. Claramunt, J. Elguero, *J. Am. Chem. Soc.* **1989**, *111*, 7348.

[112] a) *Click Reactions in Organic Synthesis*, 1ª Ed., S. Chandrasekaran, Wiley-VCH, Weinheim, Alemania, **2016**; b) *Modern Heterocyclic Chemistry*, 1ª Ed., J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Wiley-VCH, Weinheim, Alemania, **2011**.

[113] a) D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1984**, *27*, 223; b) E. C. Kohn, C. C. Felder, W. Jacobs, K. A. Holmes, A. Day, R. Freer, L. A. Liotta, *Cancer Res.* **1994**,

como anticancerígenos, antituberculosos, antibacterianos, antivirales (fundamentalmente como retroviral del VIH), antifúngicos, antituberculosos, antiepilépticos, agentes para el tratamiento de la leishmaniosis y antialérgicos. Además, se ha demostrado que este núcleo es bioisóstero del grupo funcional amida, debido a sus propiedades físico-químicas parecidas y su notable estabilidad metabólica. Por ello es utilizado en química médica como facilitadores del transporte de protones, en la construcción de racimos de glucósidos, espaciadores o enlazadores a dendrímeros, agentes de escisión del ADN, etc.[114]

Las aplicaciones del núcleo de 1,2,3-triazol no solo se limitan al campo biológico, ya que este heterociclo se encuentra presente en otros sectores de la industria química, como por ejemplo, en productos inhibidores de la corrosión en metales y aleaciones, colorantes, abrillantadores, fotoestabilizadores de materiales orgánicos y polímeros, formando parte de cristales líquidos, y agroquímicos como herbicidas, fungicidas y agentes antibacterianos para el tratamiento de plagas.[115]

En cuanto a la síntesis de este heterociclo, la metodología más popular para obtener el núcleo de 1,2,3-triazol es la reaccion de cicloadición 1,3-dipolar, entre un alquino terminal y una azida, en condiciones térmicas (Esquema II.43). Esta reacción, también conocida como cicloadición de Huisgen, se descubrió a principios del siglo XX. Inicialmente, la cicloadición [3+2] térmica de Huisgen entre azidas y

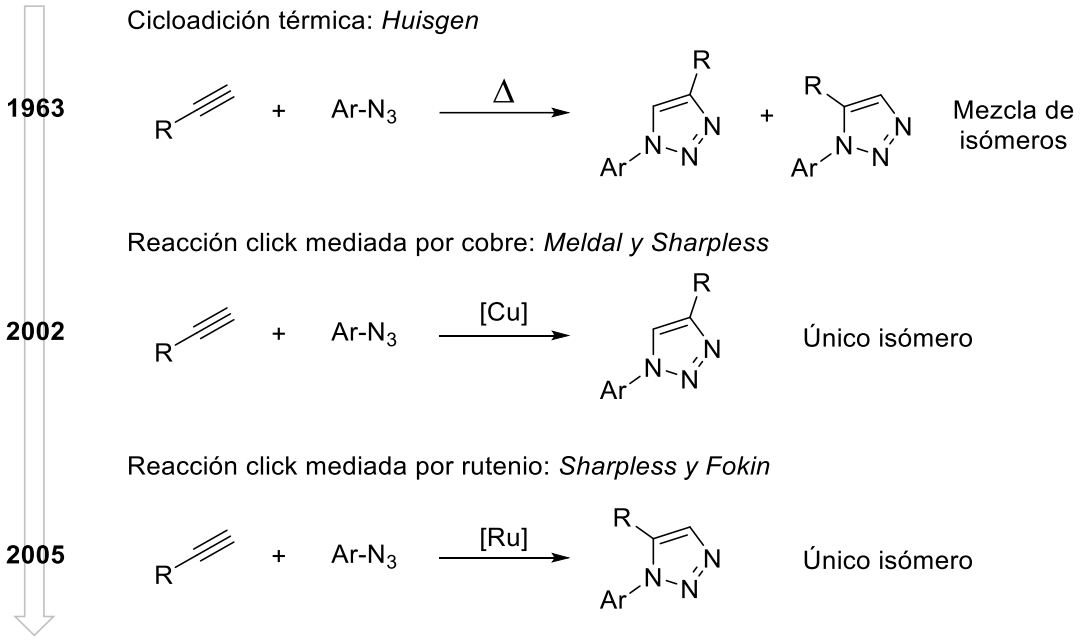
54, 935; c) S. Palhagen, R. Canger, O. Henriksen, J. A. V. Parys, M. E. Riviere, M. A. Karolchyk, *Epilepsy Res.* **2001**, *43*, 115; d) C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalker, D. Nagargoje, M. Shiradkar, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6244; e) M. J. Giffin, H. Heaslet, A. Brik, Y. C. Lin, G. Cauvi, C. H. Wong, D. E. McRee, J. H. Elder, C. D. Stout, B. E. Torbett, *J. Med. Chem.* **2008**, *51*, 6263; f) N. G. Aher, V. S. Pore, N. N. Mishra, A. Kumar, P. K. Shukla, A. Sharma, M. K. Bhat, *Bioorg. Med. Chem. Lett.* **2009**, *19*, *759*; g) J. N. Sangshetti, R. R. Nagawade, D. B. Shinde, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3564; h) J. L. Yu, Q. P. Wu, Q. S. Zhang, Y. H. Liu, Y. Z. Li, Z. M. Zhou. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 240; i) E. M. Guantai, K. Ncokaji, T. J. Egan, J. Gut, P. J. Rosenthal, P. J. Smith, K. Chibale, *Bioorg. Med. Chem.* **2010**, *18*, 8243; j) S. A. Bakunov, S. M. Bakunova, T. Wenzler, M. Ghebru, K. A. Werbovetz, R. Brun, R. R Tidwell, *J. Med. Chem.* **2010**, *53*, 254.

[114] a) P. A. Wender, S. M. Touami, C. Alayrac, U. C. Philipp, *J. Am. Chem. Soc.* **1996**, *118*, 6522; a) A. Dondoni, A. Marra, *J. Org. Chem.* **2006**, *71*, 7546; b) R. Subbaraman, H. Ghassemi, T. A. Zawodzinski, *J. Am. Chem. Soc.* **2007**, *129*, 2238; c) A. Dondoni, *Chem. Asian. J.* **2007**, *2*, 700; d) C. Ornelas, J. R. Aranzaes, L. Salmon, D. Astruc, *Chem. Eur. J.* **2008**, *14*, 50; e) C. Ornelas, J. R. Aranzaes, E. Cloutet, S. Alves, D. Astruc, *Angew. Chem. Int. Ed.* **2007**, 46, 872.

[115] a) *Science of Synthesis*, *Vol. 13, Five-Membered Hetarenes with Three or More Heteroatoms,* A. C. Tomé, R. C. Storr, T. L. Gilchrist, Georg Thieme Verlag, Stuttgart, Alemania, **2004**; b) A. J. Scheel, H. Komber, B. I. Voit, *Macromol. Rapid Commun.* **2004**, *25*, 1175; c) F. E. Gallardo, A. J. Bortoluzzi, G. Conte, *Liq. Cryst.* **2005**, *32*, 667.

alquinos no tuvo mucha utilidad sintética, debido a la escasa regioselectividad (formación de mezclas de ambos regioisómeros), bajo rendimiento y temperaturas elevadas.[116]

Afortunadamente, cuatro décadas más tarde, se retomó el estudio de esta reacción, mejorando en varios aspectos la síntesis de triazoles. En el Esquema II.43, se muestra el desarrollo cronológico del conjunto de reacciones más utilizadas en la obtención de estos heterociclos nitrogenados.



Esquema II.43

Los hallazgos de Sharpless y Meldal supusieron una revolución para la investigación del núcleo de 1,2,3-triazol. Aparte de hacer resurgir la reacción de Huisgen, estos autores introdujeron el concepto de "química clic" (*click chemistry*) en 2002.[117] Esta versión de la reacción de Huisgen se encuentra catalizada por Cu(I),

[116] a) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *75*, 565; b) *Chemistry of Alkenes*, R. Huisgen, R. Grashey, J. Sauer, Interscience, Nueva York, EEUU, **1964**.

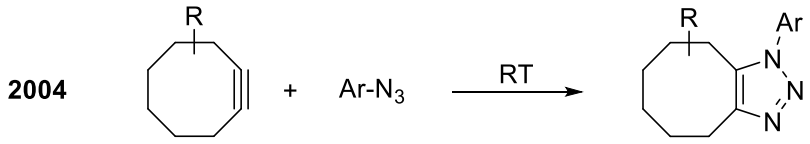
[117] a) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; c) L. V. Lee, M. L. Mitchell, S. J. Huang, V. V. Fokin, K. B. Sharpless, C. H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588; d) A. E. Speers, G. C. Adam, B. F. Cravatt, *J. Am. Chem. Soc.* **2003**, *125*, 4686; e) W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791; f) M. Whiting, J. Muldoon, Y. C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder, V. V. Fokin, *Angew. Chem. Int. Ed.* **2006**, *45*, 1435; g) H. Nandivada, X. Jiang, J. Lahann, *Adv. Mater.* **2007**, *19*, 2197; h) J. F. Lutz, Z. Zarafshani, *Adv. Drug Delivery Rev.* **2008**, *60*, 958; i) J.

lo que permite que se dé la cicloadición entre azida y alquino (*Copper-Catalyzed Azide-Alkyne Cycloaddition,* CuAAC) para producir regioselectivamente 1,2,3-triazoles 1,4-disustituidos en condiciones más suaves que las originales y con altos rendimientos (Esquema II.43).

Posteriormente, se desarrolló la reacción de cicloadición de azida-alquino catalizada por Ru(II) (*Ruthenium-Catalyzed Azide-Alkyne Cycloaddition,* RuAAC) para la síntesis regioselectiva de 1,2,3-triazoles 1,5-disustituidos (Esquema II.43),[118] es decir, permitió obtener el otro regioisómero posible de la cicloadición respecto a la catalizada por cobre. A diferencia de la reacción de CuAAC, que solo funciona en alquinos terminales, la RuAAC se aplica con éxito a alquinos internos, dando así acceso a derivados de 1,2,3-triazol totalmente sustituidos.

Debido a la toxicidad de los metales pesados para las células y biomoléculas como el ADN, la aplicación de estos métodos está limitada en la química de biomateriales y la química biológica. Para evitar el uso de metales de transición, Bertozzi y col. desarrollaron una reacción de cicloadición 1,3-dipolar entre una azida y un ciclooctino para formar 1,2,3-triazoles en ausencia de catalizadores (*Strain-Promoted Alkyne-Azide Cycloadditions*, SPAAC) (Esquema II.44).[119]

Reacción click promovida por alquinos tensionados: *Bertozzi*



Esquema II.44

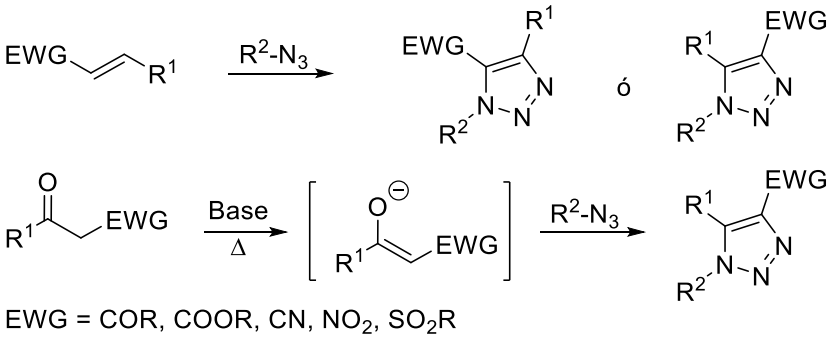
E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, *48*, 8018.

118 a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998; b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337; c) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923; d) E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, *15*, 4698.

119 a) N. J. Agard, J. A. Preschner, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046; b) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.* **2006**, 1, 644; c) J. M. Baskin, C. R. Bertozzi, *QSAR Comb. Sci.* **2007**, *26*, 1211; d) J. A. Johnson, J. M. Baskin, C. R. Bertozzi, J. T. Koberstein, N. J. Turro, *Chem. Commun.* **2008**, 3064; e) E. M. Sletten, C. R. Bertozzi, *Org. Lett*. **2008**, *10*, 3097; f) S. T. Laughlin, J. M. Baskin, S. L. Amacher, C. R. Bertozzi, *Science* **2008**, *320*, 664; g) J. C. Jewett, E. M. Sletten, C. R. Bertozzi, *J. Am. Chem. Soc.* **2010** *132*, 3688; h) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272; i) B. Gold, G. B. Dudley, I. V. Alabugin, *J. Am. Chem. Soc.* **2013**, *135*, 1558.

Esta reacción está promovida por la tendencia a liberar la tensión de anillo que supone tener un triple enlace (grupo funcional lineal) en una estructura cíclica. Sin embargo, esta reacción presenta el inconveniente de tener una regioselectividad muy limitada y la complejidad de los sustratos requeridos hace que este método no sea adecuado para aplicaciones sintéticas sencillas.

Por último, dentro de los métodos generales, encontramos aquellos basados en la reacción de cicloadición entre alquenos y azidas. El doble enlace suele estar desactivado con sustituyentes electro-atractores y puede estar presente directamente en el material de partida (sistemas α,β-insaturados) [120] o bien generarse a través de un enolato[121] intermedio sobre el que se lleva a cabo la reacción (Esquema II.45). Generalmente, estas reacciones suelen tener una regioselectividad alta.



Esquema II.45

[120] a) B. Liu, M.-X. Wang, L.-B. Wang, Z.-T. Huang, *Heteroatom Chem.* **2000**, *11*, 387; b) C. Hager, R. Miethchen, H. Reinke, *J. Fluor. Chem.* **2000**, *104*, 135; b) W. Peng, S. Zhu, *Synlett* **2003**, 187; c) W. Peng, S. Zhu, *Tetrahedron* **2003**, *59*, 4395; d) G. Adamo, F. Benedetti, F. Berti, G. Nardin, S. Norbedo, *Tetrahedron Lett.* **2003**, *44*, 9095; e) L. Vaccaro, *J. Org. Chem.* **2005**, *70*, 6526; f) B. Quiclet-Sire, S. Z. Zard, *Synthesis* **2005**, 3319; g) D. R. Roque, J. L. Neill, J. W. Antoon, E. P. Stevens, *Synthesis* **2005**, 2497; h) L. Cafici, T. Pirali, F. Condorelli, E. Del Grosso, A. Massarotti, G. Sorba, P. L. Canonico, G. C. Tron, A. A. Genazzani, *J. Comb. Chem.* **2008**, *10*, 732; i) W. Li, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 14186.

[121] a) P. Jones, M. Chambers, *Tetrahedron* **2002**, *58*, 9973; b) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Chem. Heterocycl. Compd.* **2009**, *45*, 245; c) N. T. Pokhodylo, V. S. Matiychuk, N. B. Obushak, *Chem. Heterocycl. Compd.* **2009**, *45*, 483; d) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Synthesis* **2009**, *14*, 2321; e) F. Stazi, D. Cancogni, L. Turco, P. Westerduin, S. Bacchi, *Tetrahedron Lett.* **2010**, *51*, 5385. f) A. B. Shashank, S. Karthik, R. Madhavachary, D. B. Ramachary*, Chem. Eur. J.* **2014**, *20*, 16877; g) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem. Int. Ed.* **2014**, *53*, 10420; h) P. M. Krishna, D. B. Ramachary, S. Peesapati, *RSC Adv.* **2015**, *5*, 62062; i) C. G. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixao, *Chem. Commun.* **2015**, *51*, 10784; j) D. B. Ramachary, J. Gujral, S. Peraka, G. S. Reddy, *Eur. J. Org. Chem.* **2017**, 459; k) D. B. Ramachary, G. S. Reddy, S. Peraka, J. Gujral, *ChemCatChem* **2017**, 9, 263; l) Z. E. Blastik, B. Klepetářová, P. Beier, *ChemistrySelect* **2018**, *3*, 7045.

Se han desarrollado otros muchos métodos de síntesis, pero los anteriomente comentados son los más utilizados. Con las nuevas metodologías se han introducido otros metales como el iridio,[122] uso de microondas,[123] uso de catalizadores inmovilizados y nanopartículas,[124] organocatálisis,[125] procesos libres de metales,[126] síntesis asistida por ultrasonidos,[127] procesos libres de azidas,[128] etc. Por tanto, las metodologias nuevas pueden considerarse mejoras o modificaciones de metodologías clásicas.

Dada la importarcia y utilidad de este heterociclo nitrogenado se han sintetizado 1,2,3-triazoles con todo tipo de sustituyentes para modular sus propiedades. Nuestro grupo de trabajo estaba interesado en la posibilidad de obtener 1,2,3-triazoles sutituidos por grupos sulfona mediante una cicloadición tipo azida-alqueno explotando la reactividad de la molécula de $Tf_2C{=}CH_2$.

Los triazoles sustituidos en la posición uno por una sulfona, *N*-sulfonil-1,2,3-triazoles, acaparan la mayor parte del interés en comparación con los triazoles sustituidos en las posiciones cuatro o cinco, donde también puede darse funcionalización del ciclo. En la bibliografía es posible encontrar multitud de publicaciones en torno a este tipo de triazol debido principalmente a dos factores. El primero es su facilidad sintética, pues se accede directamente por reacción

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122 S. Ding, G. Jia, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 1877.

123 a) J. F. Costa, X. G. Mera, O. Caamano, J. M. Brea, M. I. Loza, *Eur. J. Med. Chem.* **2015**, *98*, 212; b) F. B. Souza, D. C. Pimenta, H. A. Stefani, *Tetrahedron Lett.* **2016**, *57*, 1592.

124 K. Lal, P. Rani, *Arkivoc* **2016**, 1, 307.

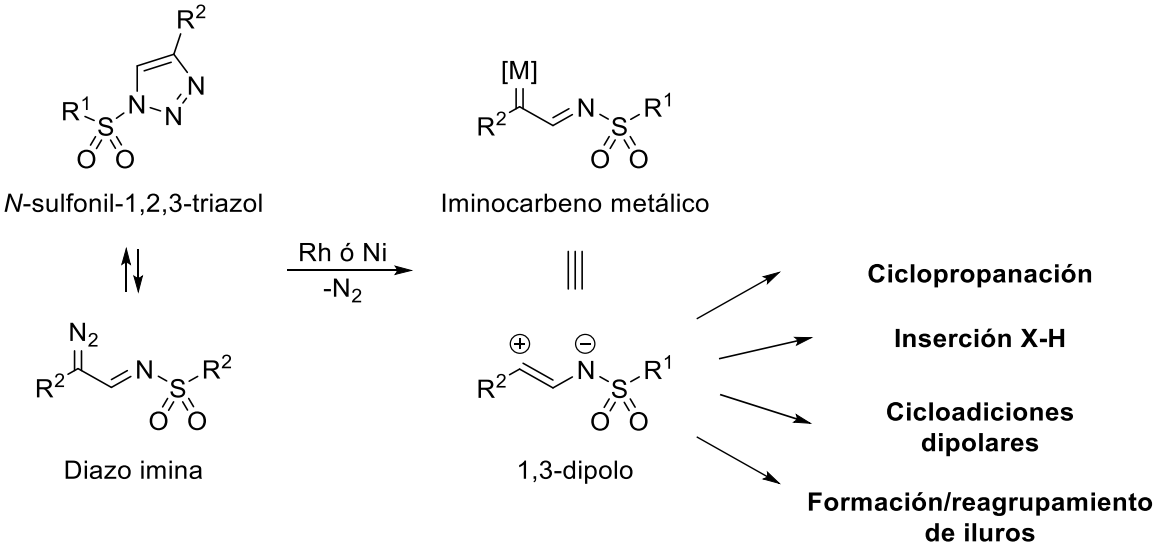
125 a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143; b) L. J. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584; c) M. Belkheira, D. El Abed, J. M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917; d) L. Wang, S. Peng, L. J. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088; e) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, *49*, 10187; f) S. S. Ramasastry, *Angew. Chem. Int. Ed.* **2014**, *53*, 14310; g) J. John, J. Thomas, W. Dehaen, *Chem. Commun.* **2015**, *51*, 10797.

126 a) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4217; b) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* **2015**, 3435; c) J. Thomas, S. Jana, J. John, S. Liekens, W. Dehaen, *Chem. Commun.* **2016**, *52*, 2885; d) H. Singh, G. Khanna, J. M. Khurana, *Tetrahedron Lett.* **2016**, *57*, 3075; e) S. Tsogoeva, H. Jalani, A. Karagöz, *Synthesis* **2016**, *49*, 29; f) M. Ahmed, H. Razaq, M. Faisal, A. N. Siyal, A. Haider, *Synth. Commun.* **2017**, *47*, 1193.

127 a) M. F. Mady, G. E. A. Awad, K. B. Jorgensen, *Eur. J. Med. Chem.* **2014**, *84*, 433; b) S. B. Nallapati, B. Y. Sreenivas, R. Bankala, K. V. L. Parsa, S. Sripelly, K. Mukkanti, M. Pal, *RSC Adv.* **2015**, 5, 94623; c) B. N. M. Silva, A. C. Pinto, F. C. Silva, V. F. Ferreira, B. V. Silva, *J. Braz. Chem. Soc.* **2016**, *27*, 2378; d) N. Rezki, *Molecules* **2016**, *21*, 1; e) D.-W. Zhang, Y.-M. Zhang, J. L., T.-Q. Zhao, Q. Gu, F. Lin, *Ultrason. Sonochem.* **2017**, *36*, 343.

128 J.-P. Wan, D. Hu, Y. Liu, S. Sheng, *ChemCatChem* **2015**, *7*, 901.

catalizada por Cu(II) entre una sulfonilazida y un alquino (materiales de partida muy accesibles) con muy buenos rendimientos. La otra razón de su popularidad, y tal vez la principal, es la interesante reactividad que presentan al producirse la apertura de anillo, que en presencia de metales (rodio y níquel fundamentalmente) forman iminocarbenos metálicos empleados en multitud de trasformaciones sintéticas (Esquema II.46).[129]



Esquema II.46

En comparación, en la bibliografía, hay pocas publicaciones sobre 4-sulfonil-1,2,3-triazoles ó 5-sulfonil-1,2,3-triazoles, principalmente porque no ofrecen un atractivo sintético comparable al de los anteriores. Aun asi, es importante ofrecer métodos para su síntesis, pues su obtención es el primer paso hacia su estudio.

Centrándonos en los 4-sulfonil-1,2,3-triazoles, que es la posición sustituida tratada en esta Tesis, encontramos algunas estructuras de interés en el campo farmacológico,[130] como por ejemplo el triazol mostrado en la Figura II.18 que presenta una potente actividad inhibitoria del transportador de glicina-1.[131]

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[129] Para una visión global de los *N*-sulfonil-triazoles y su particular reactividad, colsultar: a) A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 1371; b) H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* **2014**, *43*, 5151; c) Y. Li, H. Yang, H. Zhai, *Chem. Eur. J.* **2018**, *24*, 12757.

[130] a) S. S. Chirke, J. S. Krishna, B. B. Rathod, S. Reddy Bonam, V. M. Khedkar, B. V. Rao, H. M. S. Kumar, P. R. Shetty, *ChemistrySelect* **2017**, *2*, 7309; b) A. Ramírez-Villalva, D. González-Calderón, R. I. Rojas-García, C. González-Romero, J. Tamaríz-Mascarúa, M. Morales-Rodríguez, N. Zavala-Segoviad, A. Fuentes-Benítes, *Med. Chem. Commun*. **2017**, *8*, 2258.

[131] C. L. Cioffi, S. Liu, M. A. Wolf, P. R. Guzzo, K. Sadalapure, V. Parthasarathy, D. T. J. Loong, J.-H. Maeng, E. Carulli, X. Fang, K. Karunakaran, L. Matta, S. H. Choo, S. Panduga, R. N. Buckle,

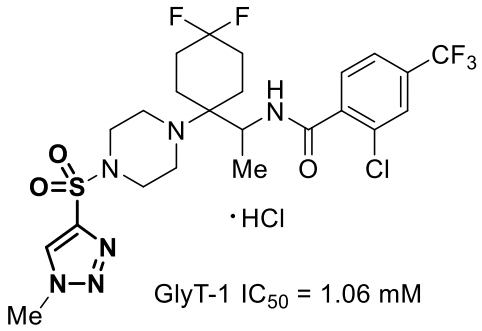
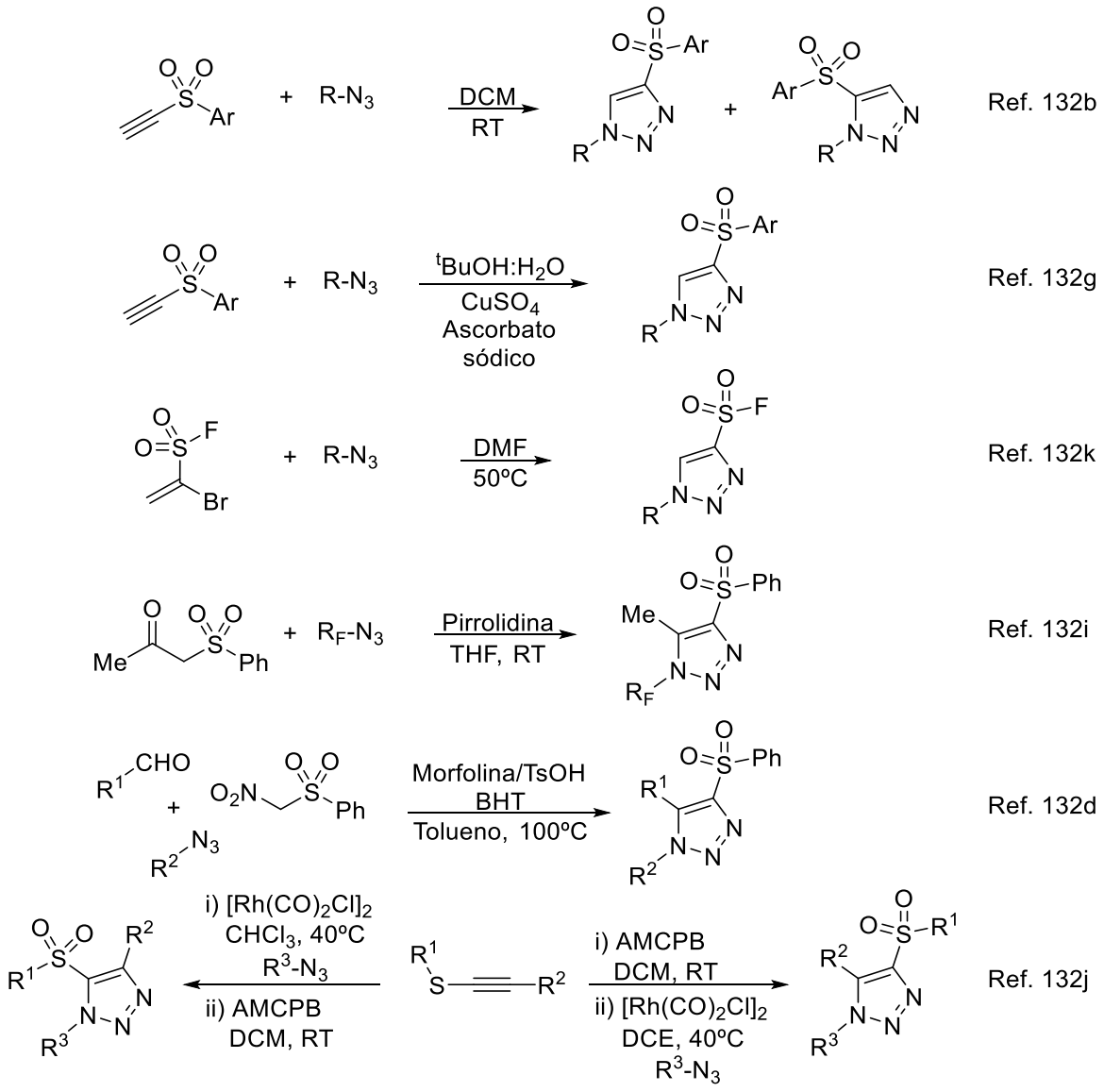


Figura II.18

Los métodos de síntesis de 4-sulfonil-1,2,3-triazoles están basados en los procedimientos clásicos.[132] En el Esquema II.47 se muestra un conjunto seleccionado de metodologías actuales usadas en su preparación.

R. N. Davis, S. A. Sakwa, P. Gupta, B. J. Sargent, N. A. Moore, M. M. Luche, G. J. Carr, Y. L. Khmelnitsky, J. Ismail, M. Chung, M. Bai, W. Yee Leong, N. Sachdev, S. Swaminathan, A. J. Mhyre, *J. Med. Chem.* **2016**, *59*, 8473.

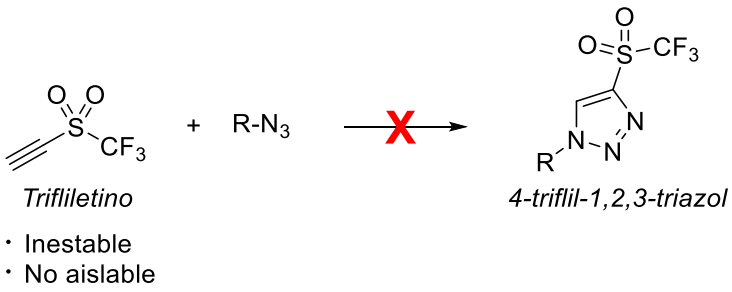
[132] a) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Synthesis* **2009**, *14*, 2321; b) S. G. Gouin, J. Kovensky, *Synlett* **2009**, *9*, 1409; c) P. N. Liu, J. Li, F. H. Su, K. D. Ju, L. Zhang, C. Shi, H. H. Y. Sung, I. D. Williams, V. V. Fokin, Z. Lin, G. Jia, *Organometallics* **2012**, *31*, 4904; d) J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem. Int. Ed.* **2014**, *53*, 10155; e) M. T. Saraiva, G. P. Costa, N. Seus, R. F. Schumacher, G. Perin, M. W. Paixao, R. Luque, D. Alves, *Org. Lett.* **2015**, *17*, 6206; f) J. John, J. Thomas, N. Parekh, W. Dehaen, *Eur. J. Org. Chem.* **2015**, 4922; g) S. S. Chirke, J. S. Krishna, B. B. Rathod, S. R. Bonam, V. M. Khedkar, B. V. Rao, H. M. S. Kumar, P. R. Shetty, *ChemistrySelect* **2017**, *2*, 7309; h) S. Narsimha, K. S. Battula, N. V. Reddy, *Heterocycl. Lett.* **2017**, *7*, 1139; i) Z. E. Blastik, B. Klepetárová, P. Beier, *ChemistrySelect* **2018**, *3*, 7045; j) W. Song, N. Zheng, M. Li, K. Dong, J. Li, K. Ullah, Y. Zheng, *Org. Lett.* **2018**, *20*, 6705; k) J. Thomas, V. V. Fokin, *Org. Lett.* **2018**, *20*, 3749.



Esquema II.47

Cuando nos interesamos en un sustituyente sulfona en particular, el trifluorometilsulfonil (-SO_2CF_3), como grupo funcional en la posición cuatro del anillo de triazol (4-triflil-1,2,3-triazoles), no encontramos ninguna referencia previa para su preparación. Intrigados por este hecho decidimos profundizar la búsqueda bibliográfica, lo que reveló que el acceso a este tipo de triazol no es posible por los métodos descritos hasta la fecha.

Por un lado, la cicloadición a partir del alquino terminal sustituido por un grupo trifluorometanosulfonilo (trifliletino) y una azida no es posible, ya que este alquino es muy reactivo e inestable (Esquema II.48).

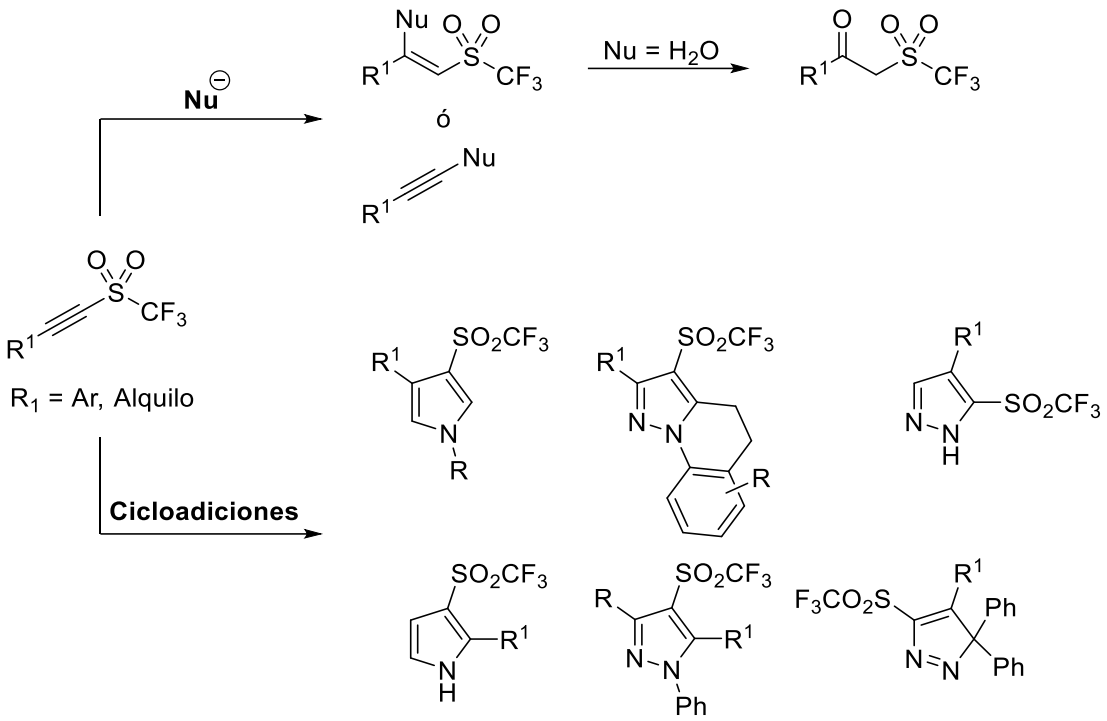


Esquema II.48

Los alquinos internos, sustituidos por un grupo Tf y un sustituyente alifático o aromático son más estables, pero siguen siendo muy reactivos, experimentando con facilidad ataques nucleófilos que producen su adición al triple enlace o la sustitución del grupo Tf.[133] De hecho, en presencia de humedad se produce fácilmente la hidratación del alquino, lo que origina la cetona correspondiente. Estas propiedades, junto a que su preparación no es trivial, hace que sea difícil trabajar con estos materiales de partida. Aun así, encontramos algunos ejemplos en los que han sido utilizados en cicloadiciones para la obtención de estructuras cíclicas;[134] entre ellas algunos heterociclos nitrogenados, pero ningún ejemplo con azidas u otros grupos funcionales para obtener 1,2,3-triazoles (Esquema II.49).

[133] a) M. Hanack, B. Wilhelm, L. R. Subramanian, *Synthesis* **1988**, *8*, 592; b) M. Hanack, B. Wilhelm, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1057; c) I. Ryu, N. Kusumoto, A. Ogawa, N. Kambe, N. Sonoda, *Organometallics* **1989**, *8*, 2279; d) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486; e) J. S. Xiang, A. Mahadevan, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4284; f) J. Xiang, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 11986; g) J. Xiang, P. L. Fuchs, *Tetrahedron Lett.* **1998**, *39*, 8597; h) J. Xiang, W. Jiang, J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1997**, *119*, 4123; c) M. Degueil-Castaing, L. Moutet, B. Maillard, *J. Org. Chem.* **2000**, *65*, 3961; i) Y. Uenoyama, T. Fukuyama, K. Morimoto, O. Nobuta, H. Nagai, I. Ryu, *Helv. Chim. Acta* **2006**, *89*, 2483; j) A. V. Vasil'ev, S. A. Aristov, G. K. Fukin, K. A. Kozhanov, M. P. Bubnov, V. K. Cherkasov, *Russ. J. Organ. Chem.* **2008**, *44*, 791; k) D. Shikanai, H. Murase, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2009**, *131*, 3166; l) V. A. Vasina, D. Yu. Korovina, I. N. Kildeeva, V. V. Razin, *Russ. J. Organ. Chem.* **2016**, *52*, 1711; m) H. Jiang, Y. He, Y. Cheng, S. Yu, *Org. Lett.* **2017**, *19*, 124; n) H.-M. Guo, Q.-Q. Zhou, X. Jiang, D.-Q. Shi, W.-J. Xiao, *Adv. Synth. Catal.* **2017**, *359*, 4141.

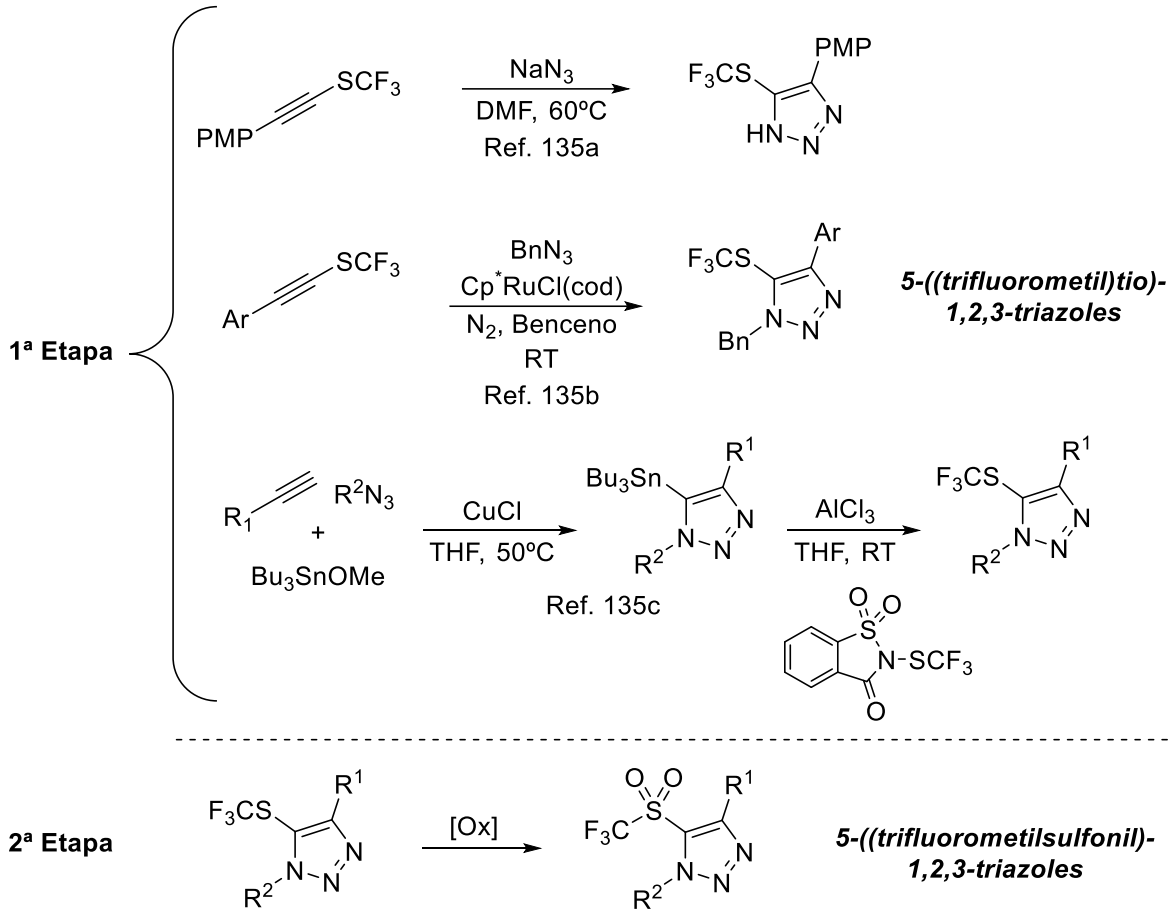
[134] a) F. Massa, M. Hanack, L. R. Subramanian, *J. Fluor. Chem.* **1982**, *19*, 601; b) S. Kosack, G. Himbert, *Chem. Ber.* **1987**, *120*, 71; c) H. C. Berk, J. E. Franz, *Synth. Commun.* **1981**, 11, 267; d) K. D. Barnes, R. Ward, *J. Heterocyclic Chem*. **1995**, 32, 871; e) H. Isobe, S. Sato, T. Tanaka, H. Tokuyama, E. Nakamura, *Org. Lett*. **2004**, 6, 3569; f) H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, *Org. Lett*. **2012**, 14, 5330; g) X. Zhou, S. Yu, Z. Qi, X. Li, *Sci. China Chem.* **2015**, 58, 8; h) V. A. Vasin, Y. A. Popkova, E. V. Bezrukova, V. V. Razin, N. V. Somov, *Russ. J. Organ. Chem.* **2017**, 53, 3, 393.



Esquema II.49

Otra estrategia sintética posible es formar los triazoles funcionalizados con el grupo trifluorometilsulfano (-SCF_3) y posterior oxidación completa del azufre a trifluorometilsulfona (-SO_2CF_3), de manera análoga al último procedimiento presentado en el Esquema II.47. Sin embargo, esta opción tampoco ha conseguido proporcionar los 4-trifluorometilsulfonil-1,2,3-triazoles. Principalmente porque los métodos disponibles para obtener los trifluorometiltio-1,2,3-triazoles precursores, sólo han conseguido obtener el isómero sustituido en la posición 5 y no en la 4,[135] lo que en el caso de producir la oxidación posterior originaría los 5-trifluorometilsulfonil-1,2,3-triazoles (Esquema II.50).

[135] a) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814; b) Q. Shena, E.-J. Hanb, Y.-G. Huang, Q.-Y. Chen, Y. Guo, *Synthesis* **2015**, *47*, 3936; c) F. Wei, T. Zhou, Y. Ma, C.-H. Tung, Z. Xu, *Org. Lett.* **2017**, *19*, 2098.



Esquema II.50

Tras todo lo anteriormente comentado, nos dimos cuenta que la molécula de $Tf_2C{=}CH_2$ podía ser una excelente candidata para llevar a cabo una cicloadición con azidas, y obtener fácilmente y en un paso de reacción los esquivos 4-triflil-1,2,3-triazoles. Bajo esta premisa se desarrolló el trabajo que ha dado lugar al último Capítulo 8 de la presente Memoria y que será comentado en detalle en su apartado correspondiente de la Discusión General.

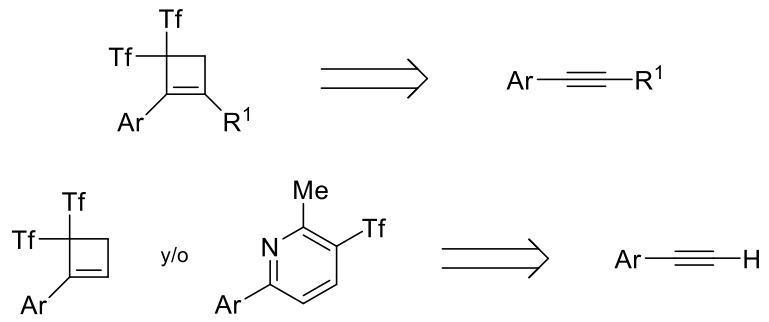
III. OBJETIVOS

III. OBJETIVOS

La presente Tesis Doctoral tiene como Objetivo General estudiar las aplicaciones sintéticas que pueden ofrecer los zwitteriones de Koshar. Estos zwitteriones son portadores de una molécula altamente polarizada latente que puede actuar como un 1,2-dipolo o como un aceptor de Michael. Se determinará la reactividad que presentan frente a diferentes sistemas insaturados y diversos heterociclos.

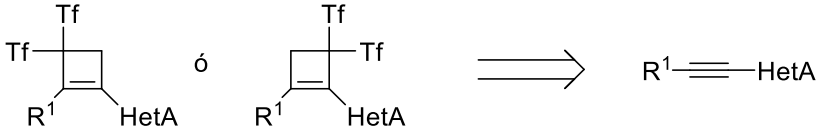
Para alcanzar este Objetivo General, la presente Memoria se ha divido en ocho Capítulos, en los que se desarrollan las ocho publicaciones a las que han dado lugar los resultados obtenidos, seguidos de una Discusión General de los mismos y las Conclusiones finales.

En el Capítulo 1 se estudiará la reactividad que presentan los zwitteriones de Koshar frente a alquinos simples, mono- y disustituidos con restos aromáticos y alifáticos (Esquema III.1).



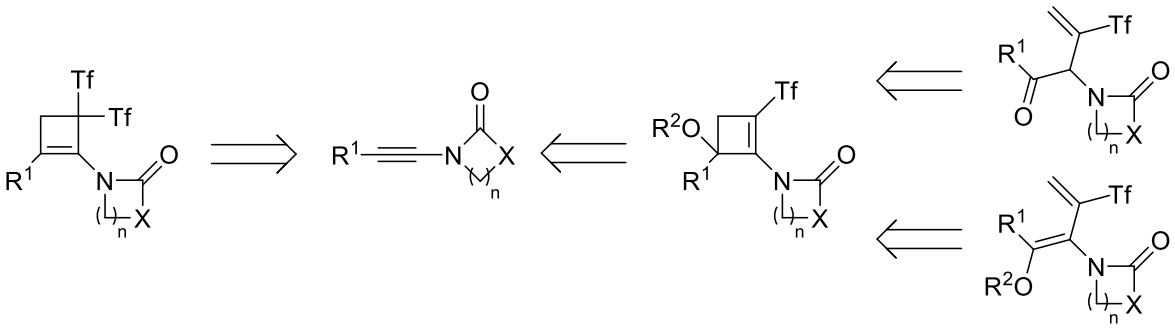
Esquema III.1

En el Capítulo 2 se extenderá la metodología del Capítulo 1 a alquinos más complejos, sustituidos por heteroátomos, determinando como afecta este hecho a la reactividad, quimioselectividad y regioselectividad (Esquema III.2).



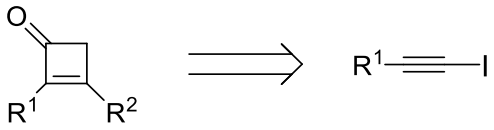
Esquema III.2

En el Capítulo 3 se estudiará una clase específica de alquinos, las inamidas. Se verá cuál es su comportamiento frente a los zwitteriones de Koshar y cómo los sustituyentes modifican de manera selectiva el producto final formado. Además, se demostrará la utilidad sintética de algunos compuestos obtenidos (Esquema III.3).



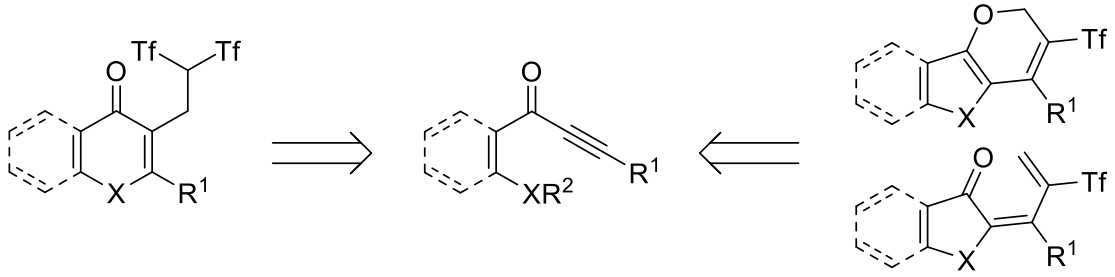
Esquema III.3

En el Capítulo 4, a partir de yodoalquinos, estudiados en Capítulo 2, se mostrará una metodología directa para utilizarlos como materiales de partida en la obtención de ciclobutenonas (Esquema III.4).



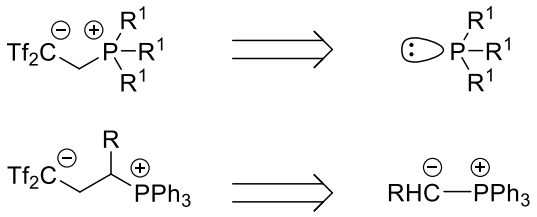
Esquema III.4

En el Capítulo 5, se presentará el estudio realizado sobre inonas, alquinos funcionalizados que muestran una reactividad muy diferenciada del resto de alquinos estudiados. Además, modulando la temperatura y el disolvente será posible obtener dos tipos de heterociclos completamente diferentes a partir de la misma inona de partida (Esquema III.5).



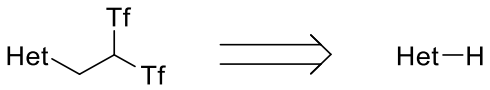
Esquema III.5

En el Capítulo 6 se abordará el último alquino funcionalizado estudiado, las alquinilfosfinas. Junto a otros tipos de fosfinas e iluros de fósforo, con comportamiento similar, se estudiará su reactividad y sus propiedades estructurales a través de diferentes técnicas (Esquema III.6).



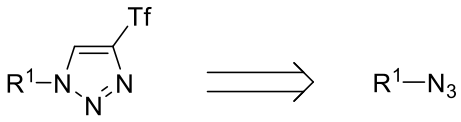
Esquema III.6

El Capítulo 7 tratará el uso de los zwitteriones de Koshar como agentes alquilantes de heterociclos ricos en electrones, y su aplicación a casos concretos para demostrar su utilidad (Esquema III.7).



Esquema III.7

Por último, el Capítulo 8 abordará el uso de los zwitteriones de Koshar en la preparación de triazoles a partir de azidas, permitiendo el control de la quimioselectividad en función de su naturaleza (Esquema III.8).



Esquema III.8

IV. CAPÍTULO 1

IV.1. Unveiling the Uncatalyzed Reaction of Alkynes with 1,2-Dipoles for the Room Temperature Synthesis of Cyclobutenes

2-(Pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free direct [2+2] cycloaddition reaction of alkynes. Starting from stable zwitterionic pyridinium salts, the electron deficient olefin 1,1-bis(trifluoromethylsulfonyl)ethene is generated in situ and immediately reacted at room temperature with an alkyne to afford substituted cyclobutenes. Remarkably, this mild and facile uncatalyzed protocol requires neither irradiation nor heating.

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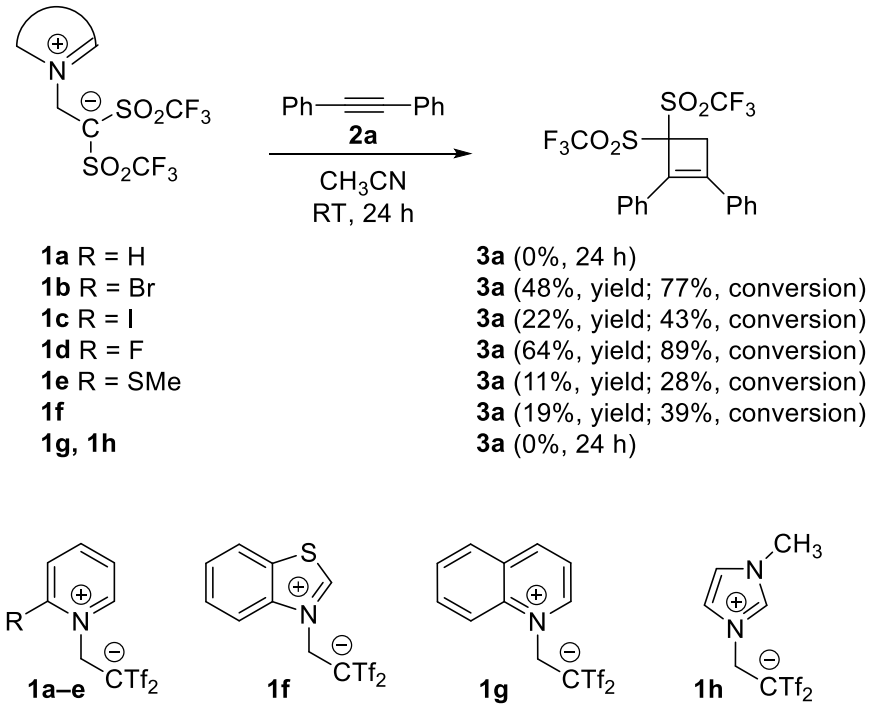
IV.2. Communication

Cyclobutene derivatives are attractive compounds both as target molecules as well as useful building blocks for the construction of more complex structures.[1–7] The most popular method for cyclobutene preparation in a single step is the [2+2] cycloaddition reaction of alkynes with unsaturated systems.[8] The [2+2] cycloaddition of alkynes with alkenes has been studied both under photochemical or thermal conditions as well as by transition-metal catalysis. Because the thermal [π2s + π2s] transformation is a forbidden process according to the Woodward-Hoffmann orbital symmetry principles,[9] in most cases the occurrence of discrete diradical or ionic intermediates has been suggested for both thermal and photoinitiated [2+2] reactions. Despite that, these traditional protocols present serious drawbacks because: (a) modest yields are usually encountered; and (b) either photochemical or strong thermal conditions are required, which may be incompatible with selectivity control as well as sensitive functional groups. Although metal-catalyzed strategies have merged recently, their widespread use in cyclobutene synthesis is precluded due to the narrow substrate scope and moderate selectivity,[10–13] or because of the use of environmentally unsafe or expensive transition-metal salts.[14–17]

Alkynes are useful starting materials for the preparation of a variety of different compounds,[18,19] and when used as reactants in 1,3- dipolar cycloaddition reactions they typically afford five-membered cycles. By analogy, the reaction of alkynes with 1,2-dipoles through a 1,2-dipolar cycloaddition reaction may be a possible solution to produce cyclobutenes with high reaction efficiency.[20] However, this synthetic achievement has not yet been accomplished mainly due to the lack of synthetic methods allowing facile access to 1,2-dipoles. We describe herein the uncatalyzed reaction of alkynes with the 1,2-dipole 1,1-bis(trifluoromethylsulfonyl)ethene, as a straightforward route towards cyclobutenes at room temperature.

In order to achieve a practical and convenient synthesis of cyclobutenes from alkynes, a facile access to the 1,2-dipole partner, namely, the highly polarized $Tf_2C{=}CH_2$ reagent is required. Noticeably, azolium salts **1a–h** (Scheme IV.1) have been identified as stable precursors of the 1,1-bis(trifluoromethylsulfonyl)ethane species.[21]

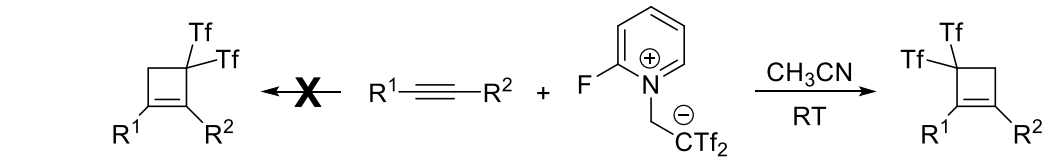


Scheme IV.1. Room temperature uncatalyzed synthesis of diphenyl cyclobutene **3a** using differently substituted zwitterions **1**.

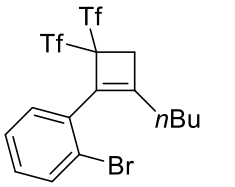
1,2-Diphenylethyne **2a** was then selected to test the cyclobutene formation through its reaction with 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanide **1a**. Disappointingly, cyclobutene was not formed in the event. Much to our delight, modification of the electronic nature of derivative 1 by using differently substituted pyridinium and azolium salts was highly beneficial, because the bromoderivative **1b** gave the cyclobutene **3a** in a fair 48% isolated yield. Even better results (64% yield) were obtained with the fluoropyridinium **1d** (Scheme IV.1). It is worth noting that the formation of cyclobutene **3a** was successfully carried out at room temperature with no requirements for the catalyst, light or heating sources. The formal [2+2] cycloadditon reaction was optimized in the absence of any additive by systematically changing several reaction parameters. Upon changing the solvent polarity, the efficiency of the reaction changed slightly. Lower reaction yields and recovery of the starting material were observed using DMSO, DMF or THF. It was found that the reaction in the initially selected solvent acetonitrile gave the best results. Among all the temperatures examined, room temperature proved to be the best choice, affording cyclobutene **3a** in a reasonable 64% yield. Finally as observed, the optimal

reaction conditions for the cyclobutene formation turned out to be 2-(2-fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1 equiv.) with the appropriate alkyne (1 equiv.), at room temperature in acetonitrile.

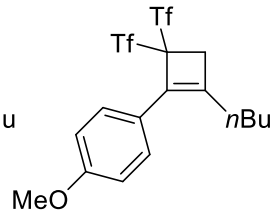
Having identified the optimized reaction conditions we proceeded to study the alkyne scope to further expand the synthetic utility of the process (Scheme IV.2). A variety of aliphatic, aromatic, and heteroaromatic substituents were well tolerated. Furthermore, non-symmetrical disubstituted alkynes could be successfully used in this intermolecular cyclization reaction. The steric properties of the substituents in the acetylenic moiety did not affect significantly the yield, with 2-aryl functionalized alkyne **2b** performing well in the cyclobutene **3b** formation. The electronic nature of the substituents did appear to have an influence on the course of the reaction. Compared to alkynes having electron-withdrawing substituents, alkynes bearing electron-donating groups gave us better results as far as conversions are concerned. Thus, the electronically rich methoxy derivative **2c** afforded the corresponding cyclobutene **3c** in much better isolated yield than its nitro counterpart (*e.g.* **2d**). Notably, the regioselectivity was perfect, provided that the substituents at both alkynic sides were different. When a strained cyclopropyl substituent was introduced at the alkyne, the desired cyclobutene still formed (*e.g.* **3e** and **3f**). Interestingly, the mildness of the protocol allows the reaction of internal alkynes phenylprop-2-yn-1-ol **2g** and 1-(3-hydroperoxyprop-1-ynyl)-4-methoxybenzene **2h** bearing sensitive functionalities to be converted into functionalized cyclobutenes **3g** and **3h** in good yields (Scheme IV.2). Besides alkynes possessing arylacetylene moieties, substrates with heteroaromatic substituents were also investigated. Substrates having a π-excedent heterocycle (*e.g.* **2i** and **2j**) provided the desired cyclobutene (*e.g.* **3i** and **3j**) in good yields (Scheme IV.2); however, when the thiophene ring was replaced with a π-deficient heterocycle (*e.g.* pyridine), the corresponding cyclobutene was not formed. This phenomenon could be readily understood by considering that an alkyne bearing an electron-rich substituent is more nucleophilic than an alkyne bearing an electron-poor substituent and hence the former is more prone to attack intermolecularly to the nascent zwitterion 1,1-bis(trifluoromethylsulfonyl)ethene. 2-[2-(Aryl)cyclobut-1-enyl]tetrahydrofuran **3k** was also obtained in an efficient manner from alkyne **2k** (Scheme IV.2).



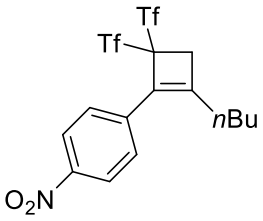
2b–o **1d** **3b–o**



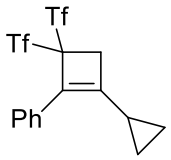
3b (59%, 5 h)



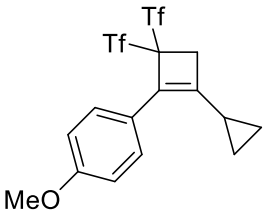
3c (96%, 5 h)



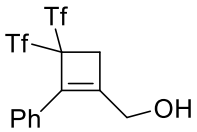
3d (25%, yield based on conversion: 64%, 24 h)



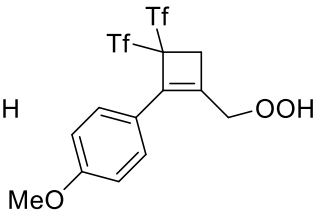
3e (41%, yield based on conversion: 73%, 24 h)



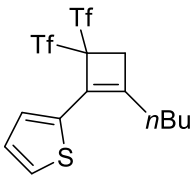
3f (51%, yield based on conversion: 77%, 12 h)



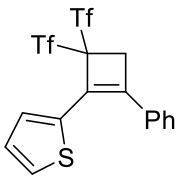
3g (72%, 12 h)



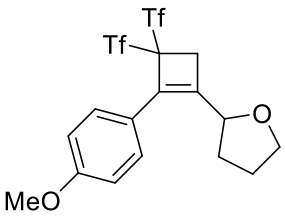
3h (68%, 5 h)



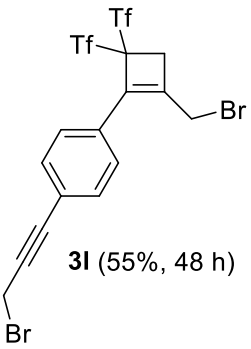
3i (74%, 4 h)



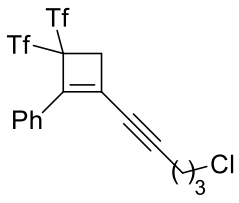
3j (56%, 24 h)



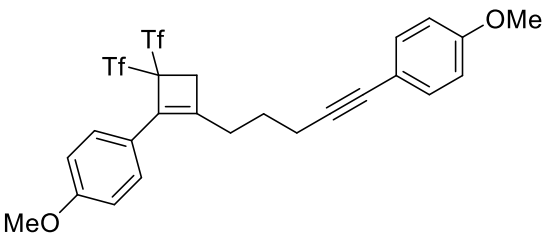
3k (75%, 5 h)



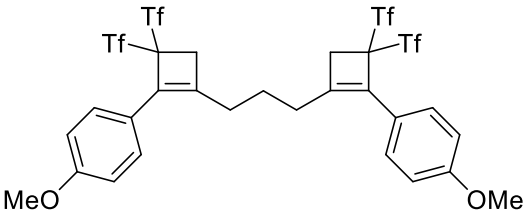
3l (55%, 48 h)



3m (53%, 48 h)



3n (47%, 4 h)

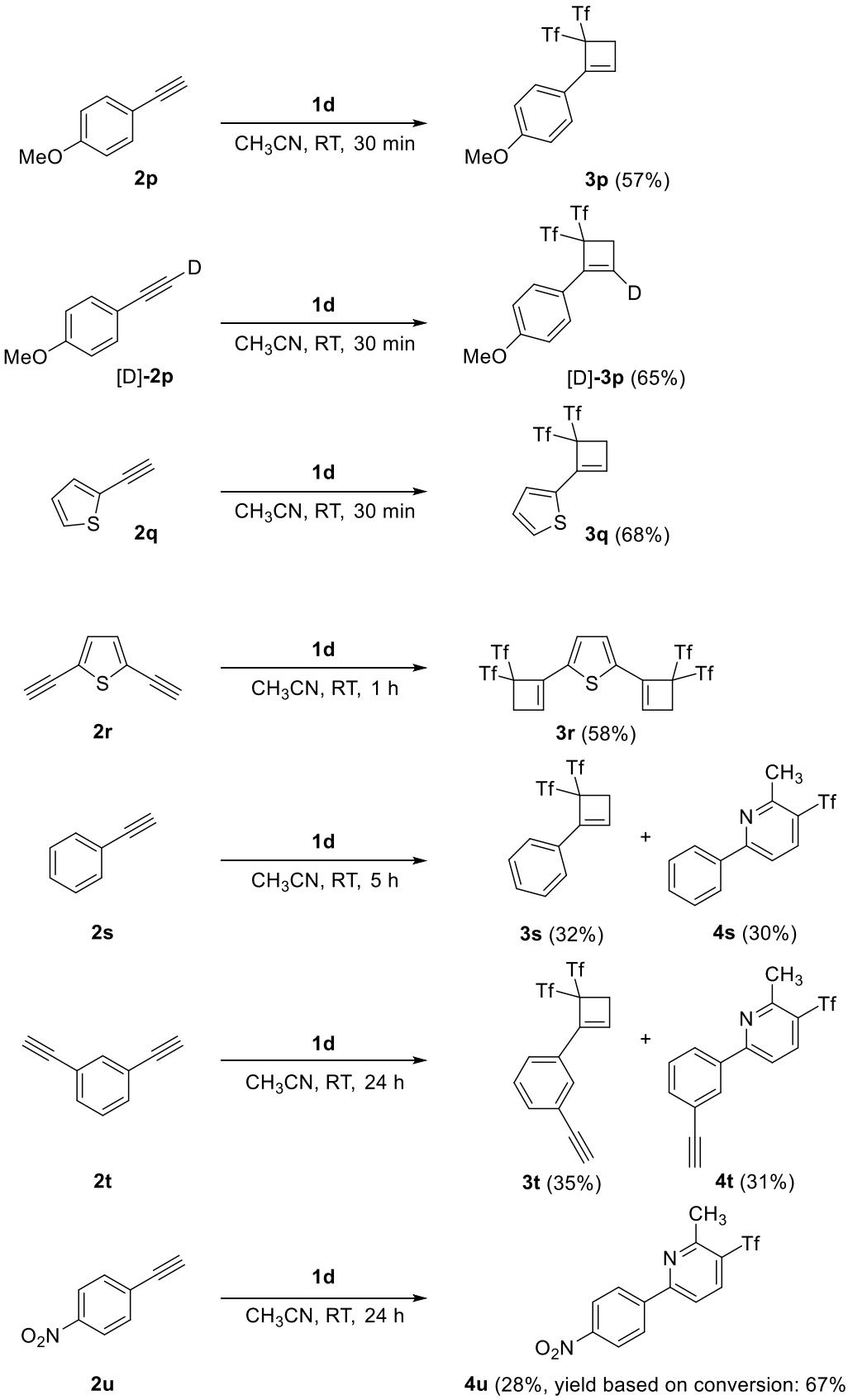


3o (86%, 4 h)

Scheme IV.2. Room temperature uncatalyzed synthesis of cyclobutenes **3b–o** from differently substituted alkynes **2**.

The selective monofunctionalization of diynes **2l–n** into cyclobutenes **3l–n** as well as the two-fold reaction to form bis(cyclobutene) **3o** from diyne **2n** were also successfully developed (Scheme IV.2). Interestingly, the mildness of the protocol allows the control of both the mono and the double reaction of diyne **2n** (Scheme IV.2). As shown in Scheme IV.2, the above process in a one-pot operation from readily available alkynes and 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides serves as a general approach towards polysubstituted cyclobutenes. Besides, cyclobutenes **3b–o** could be obtained in good yields and with total regioselectivity. Because cyclobutenes are of high synthetic utility, it was desirable to scale up the procedure in order to obtain gram quantities. It is worth noting that when we performed a 5 mmol-scale reaction starting from alkyne **2g**, cyclobutene **3g** was isolated in a yield of 77%, which is slightly higher than that achieved at a smaller scale during the scope study. For conclusive assessment of the structure of compounds **3** the X-ray crystallographic analysis of the crystals of cyclobutene **3c** was undertaken.[22]

Encouraged by the results obtained in our above method, we focused our attention as well on terminal alkynes, which are generally less reactive. Terminal aliphatic alkynes failed to react and the starting material was recovered unchanged under these conditions. However, 1-ethynyl-4-methoxybenzene **2p** and 1-(ethynyl-*d*)-4-methoxybenzene [D]-**2p** were subjected to the optimized conditions and the corresponding cyclobutenes **3p** and [D]-**3p** were smoothly formed in satisfactory yields (Scheme IV.3). Nicely, the presence of a deuterium atom at the terminal end of the alkyne does not affect the efficiency of the reaction, which may allow the synthesis of deuterated cyclobutenes. In a similar manner 2-ethynylthiophene **2q** and 2,5-diethynylthiophene **2r** reacted with 1,1-bis(triflyl)ethanide **1d** to produce cyclobutene **3q** and bis(cyclobutene) **3r** in reasonable yields (Scheme IV.3). For terminal alkynes, the acetylene moiety with an electron-donating group on the arene exhibited higher reactivity and required shorter time for completion than that of internal alkynes; probably due to steric reasons. The reaction of phenylacetylene **2s** also worked well and provided the product **3s** along with an unexpected product, the pyridine **4s** (Scheme IV.3).



Scheme IV.3. Preparation of cyclobutenes **3p–t** and pyridines **4s–u** from terminal alkynes.

1,3-Diethynylbenzene **2t** bearing an extra terminal alkyne, also reacted similarly and provided cyclobutene **3t** and pyridine **4t** in a 1:1 ratio (Scheme IV.3). Although there is absence of chemoselectivity for alkynes **2s** and **2t**, it is worth noting that cyclobutenes **3s**,**t** and pyridines **4s**,**t** are easily separated, thus providing readily two valuable cyclic products. Interestingly, nitroaryl substitution in the terminal alkyne did alter the reaction, which exclusively yielded the pyridine adduct **4u** (Scheme IV.3), but considerable amounts of starting alkyne **2u** remained unaffected under the reaction conditions. The formation of pyridines **4** may be explained taking into account the participation of the solvent (acetonitrile) as the coupling partner. These results suggest that for terminal alkynes, the presence of an electron-donating substituent critically influences the formation of the desired cyclobutene.

Density Functional Theory (DFT) calculations were carried out at the PCM(acetonitrile)-M06-2X/6-31+G(d) level to gain more insight into the above described reaction between alkynes and azolium salts **1**. To this end, we considered the reaction involving phenylacetylene **2s** and **1d** in the presence of MeCN, which leads to the formation of cyclobutene **3s** and pyridine **4s** in *ca*. 1:1 ratio. The corresponding computed reaction profiles are shown in Figure 1, which gathers the relative free energies computed at 298 K (ΔG_{298}). Our calculations suggest that the process begins with the formation of 1,1-bis(trifluoromethylsulfonyl)ethene (**INT1**) from **1d**. This initial reaction step occurs *via* the transition state **TS1**, associated with the C···N dissociation, with an activation barrier of only 11.9 kcal mol^{-1} in a slightly endergonic transformation (ΔG_R = 4.8 kcal mol^{-1}). The 1,2-dipole nature of ethene **INT1** is confirmed by the NBO-charges computed at both carbon atoms (+0.37 and −0.70 e, respectively).[23] As a consequence, a stepwise [2+2]-cycloaddition reaction with alkyne **2s** is expected to take place. Indeed, we were able to locate on the potential energy surface of the transition state **TS2**, a saddle point associated with the nucleophilic addition of the terminal carbon atom of alkyne **2s** to the positively charged carbon atom of the dipole **INT1**. This C···C bond forming process, which leads to the zwitterionic intermediate **INT2**, proceeds with an activation barrier of 17.6 kcal mol^{-1}. Interestingly, the addition involving the internal carbon atom of the alkyne proceeds *via* **TS2-B** with a much higher activation barrier ($\Delta G^{‡}_{298}$ = 35.7 kcal mol^{-1}), which makes this alternative nucleophilic addition unfeasible at room temperature. This finding explains the extraordinary regioselectivity of the transformation

experimentally observed. Finally, cyclobutene **3s** is formed through a ring-closure reaction *via* **TS3**. The ease of this final reaction step becomes evident from the computed high exergonicity (ΔG_R = −28.1 kcal mol^{-1}) and low activation barrier ($\Delta G^{\ddagger}_{298}$ = 3.0 kcal mol^{-1}) associated with this ring-closure.

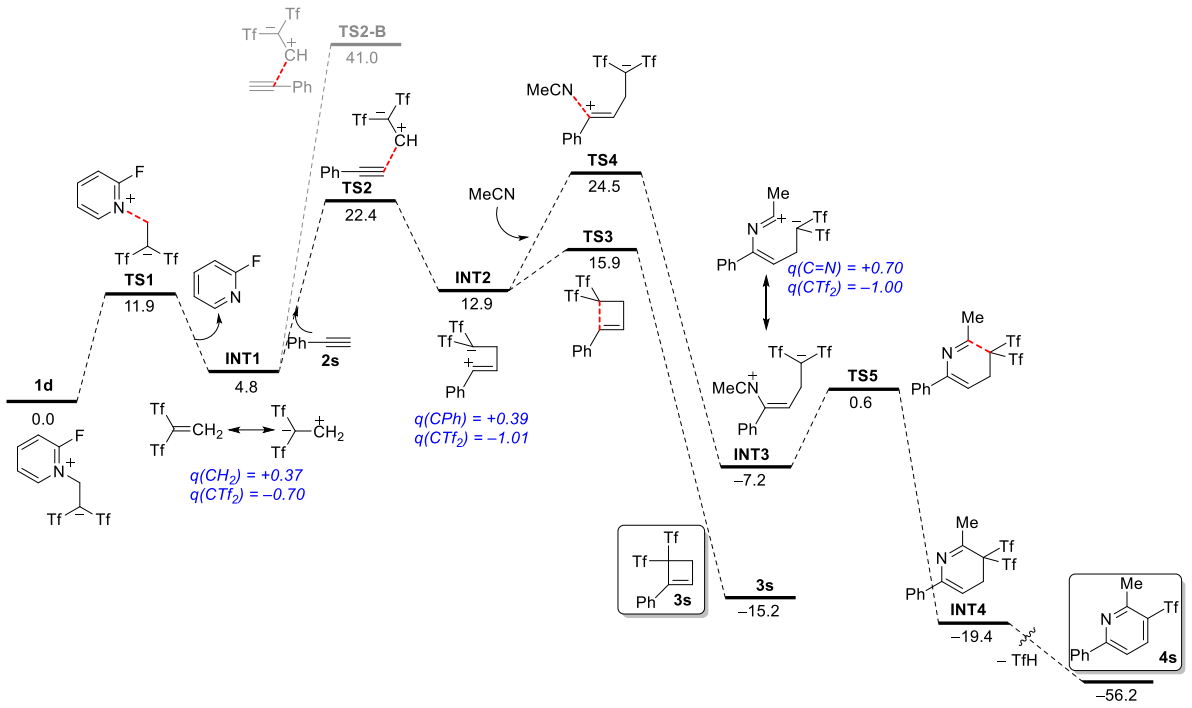


Figure 1. Computed reaction profile for the reaction between **2s** and **1d**. Relative free energies (ΔG_{298}, at 298 K) are given in kcal mol^{-1}. All data have been computed at the PCM(acetonitrile)-M06-2X/6-31+G(d) level.

The formation of pyridine **4s** necessarily involves the participation of the solvent MeCN as a nucleophile. Thus, zwitterion **INT2** is able to react with MeCN to produce the new zwitterionic intermediate **INT3** *via* **TS4** ($\Delta G^{\ddagger}_{298}$ = 11.6 kcal mol^{-1}) in an exergonic transformation (ΔG_R = −20.1 kcal mol^{-1}). A subsequent ring-closure via **TS5** ($\Delta G^{\ddagger}_{298}$ = 11.6 kcal mol^{-1}) leads to the 3,4-dihydropyridine **INT4**, which rapidly evolves to the final pyridine **4s** by TfH elimination in a strongly exergonic transformation (ΔG_R = −49.0 kcal mol^{-1}). The driving-force of this process is clearly related to the gain in aromaticity associated with pyridine formation. Despite that, from the data in Figure 1 it becomes clear that the stepwise [2+2]-cycloaddition reaction is kinetically favoured over the pyridine formation and for this reason, the exclusive formation of cyclobutenes **3** is observed experimentally in most of the reactions studied (Schemes 2 and 3).

In conclusion, 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free stepwise [2+2]-cycloaddition reaction of alkynes. The great advantage of this method is the easy synthesis of substituted cyclobutenes from readily available and stable precursors under mild conditions. Remarkably, this smooth and facile uncatalyzed protocol requires neither irradiation nor heating. Besides, this protocol has successfully overcome the challenges of earlier methods regarding selectivity of the products.

IV.3. Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Xcalibur, Atlas CCD, difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 40 mA with an exposure of 30.18 s in ω. All commercially available compounds were used without further purification.

Azolium salts **1a**, **1b**, **1d**, **1f**, and **1h** were synthesized according to a literature procedure: H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi, T. Matsumoto, *Chem. Commun.* **2013**, *49*, 10091. Novel azolium salts **1c**, **1e**, and **1g** were also prepared using the above standard procedure.

General procedure for the synthesis of azolium salts 1. To a solution of bis[(trifluoromethyl)sulfonyl]methane (1.0 mmol) in 1,2-dichloroethane (6.0 mL), paraformaldehyde (90% purity, 2.0 mmol) and the appropriate azaheterocycle (2 mmol) were sequentially added at room temperature. After being stirred at 60°C (typically 4–8 h), the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with $CHCl_3$ (3x1.0 mL) to give the corresponding azolium salt **1** as solid. Spectroscopic and analytical data for previously unreported azolium salts **1c**, **1e**, and **1g** follow.

Azolium salt 1c. From 290 mg (1.44 mmol) of 2-iodopyridine, compound **1c** (310 mg, 90%) was obtained as a colorless solid; mp 160–162 ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 5.67 (br s, 2H, CH_2), 8.06 (m, 2H, $2CH^{Ar}$), 8.52 (m, 1H, CH^{Ar}), 9.40 (m, 1H, CH^{Ar}); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 146.4 (CH^{Ar}), 145.6 (CH^{Ar}), 142.6 (CH^{Ar}), 128.5 (CH^{Ar}), 121.6 (q, J_{CF} = 325.7 Hz, $2CF_3$), 115.8 (C^{q}), 69.6 (CH_2), 68.9 (CTf_2); ^{19}F NMR (CD_3CN): δ = –80.7 (s, 6F, $2CF_3$); IR (KBr): ν = 1346, 1100 (O=S=O), 1191 (C–F) cm^{-1}; HRMS (ES): calcd for C_5H_4NI [M – $C_4H_2F_6O_4S_2$]$^{+}$: 204.9388; found: 204.9390.

Azolium salt 1e. From 180 mg (1.44 mmol) of 2-methylthiopyridine, compound **1e** (350 mg, 99%) was obtained as a colorless solid; mp 190–192 ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 2.85 (s, 3H, SCH_3), 5.41 (br s, 2H, CH_2), 7.77 (t, 1H, J = 7.0 Hz, CH^{Ar}), 7.84 (d, 1H, J = 8.4 Hz, CH^{Ar}), 8.28 (m, 1H, CH^{Ar}), 9.14 (d, 1H, J = 6.4 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 161.5 (C^{q}), 144.2 (CH^{Ar}), 143.3 (CH^{Ar}), 125.5 (CH^{Ar}), 122.8 (CH^{Ar}), 121.6 (q, J_{CF} = 325.7 Hz, $2CF_3$), 66.1 (CTf_2), 58.5 (CH_2), 16.5 (SCH_3); ^{19}F NMR (CD_3CN): δ = –80.6 (s, 6F, $2CF_3$); IR (KBr): ν = 1359, 1094 (O=S=O), 1198 (C–F) cm^{-1}; HRMS (ES): calcd for C_6H_7NS [M – $C_4H_2F_6O_4S_2$]$^{+}$: 125.0299; found: 125.0304.

Azolium salt 1g. From 190 mg (1.44 mmol) of benzothiazole, compound **1g** (280 mg, 91%) was obtained as a colorless solid; mp 181–183 ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 5.72 (s, 2H, CH_2), 7.90 (t, 1H, J = 7.7 Hz, CH^{Ar}), 8.00 (t, 1H, J = 7.9 Hz, CH^{Ar}), 8.37 (d, 1H, J = 8.3 Hz, CH^{Ar}), 8.52 (d, 1H, J = 8.5 Hz, CH^{Ar}), 10.27 (s, 1H, CH^{Ar}); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 163.5 (CH^{Ar}), 141.2 (C^{q}), 132.5 (C^{q}), 130.9 (CH^{Ar}), 129.9 (CH^{Ar}), 125.5 (CH^{Ar}), 121.6 (q, J_{CF} = 325.6 Hz, $2CF_3$), 118.3 (CH^{Ar}), 66.6 (CTf_2), 54.2 (CH_2); ^{19}F NMR (CD_3CN): δ = –81.0 (s, 6F, $2CF_3$); IR (KBr): ν = 1350, 1103 (O=S=O), 1170 (C–F) cm^{-1}; HRMS (ES): calcd for C_7H_5NS [M – $C_4H_2F_6O_4S_2$]$^{+}$: 135.0143; found: 135.0141.

General procedure for the synthesis of cyclobutenes 3. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1.0 mmol) was added at room temperature to a solution of the appropriate alkyne **2** (1.0 mmol) in acetonitrile (8.0 mL). After disappearance of the starting material (TLC) the mixture was concentrated under reduced pressure. Chromatography of the residue gave analytically pure compounds. Spectroscopic and analytical data for cyclobutenes **3** follow.

Cyclobutene 3a. From 30 mg (0.17 mmol) of alkyne **2a**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (95:5) as eluent gave compound **3a** (50 mg, 64%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 3.28 (s, 2H, CH_2), 6.82 (m, 2H, $2CH^{Ar}$), 6.95 (m, 6H, $6CH^{Ar}$), 7.64 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 151.1 (*C*=C-CH_2), 131.2 (CH^{Ar}), 130.9 (C=*C*-CH_2), 130.8 (C^{q}), 130.1 (CH^{Ar}), 127.9 (C^{q}), 129.1 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 128.8 ($2CH^{Ar}$), 127.5 ($2CH^{Ar}$), 120.4 (q, J_{CF} = 331.4 Hz, $2CF_3$), 88.3 (CTf_2), 34.5 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.40 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1380, 1104 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{12}O_4S_2F_6$ [*M*]$^{+}$: 470.0081; found: 470.0077.

Cyclobutene 3b. From 40 mg (0.17 mmol) of alkyne **2b**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3b** (53 mg, 59%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.87 (t, 3H, *J* = 7.2 Hz, CH_3), 1.34 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 2.40 (t, 2H, *J* = 7.6 Hz, CH_2), 3.35 (s, 2H, CH_2-*allylic*), 7.26 (td, 1H, *J* = 7.7, 1.7 Hz, CH^{Ar}), 7.36 (td, 1H, *J* = 7.6, 1.3 Hz, CH^{Ar}), 7.58 (dd, 1H, *J* = 7.8, 1.7 Hz, CH^{Ar}), 7.65 (dd, 1H, *J* = 8.0, 1.2 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.6 [*C*=C-$(CH_2)_3CH_3$], 133.3 (CH^{Ar}), 131.0 (CH^{Ar}), 130.8 (C^{q}), 130.6 (CH^{Ar}), 130.3 (C^{q}), 125.2 (CH^{Ar}), 123.8 [C=*C*-$(CH_2)_3CH_3$], 119.7 (q, J_{CF} = 331.3 Hz, $2CF_3$), 88.1 (CTf_2), 35.0 (CH_2-*allylic*), 30.8 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 13.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.6 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1381, 1106 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{15}O_4S_2F_6Br$ [*M*]$^{+}$: 527.9499; found: 527.9473.

Cyclobutene 3c. From 40 mg (0.21 mmol) of alkyne **2c**, and after chromatography of the residue using hexanes/diethyl ether (9:1) as eluent gave compound **3c** (97 mg, 96%) as a colorless solid; mp 59–61 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.95 (t, 3H, *J* = 7.2 Hz, CH_3), 1.42 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.55 (t, 2H, *J* = 7.6 Hz, CH_2), 3.34 (s, 2H, CH_2-*allylic*), 3.84 (s, 3H, OCH_3), 6.93 (m, 2H, $2CH^{Ar}$), 7.50 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.2 (C^{q}-OCH_3), 154.9 [*C*=C-$(CH_2)_3CH_3$], 131.7 [C=*C*-$(CH_2)_3CH_3$], 129.4 ($2CH^{Ar}$), 122.3 (C^{q}), 119.8 (q, J_{CF} = 331.4 Hz, $2CF_3$), 114.0 ($2CH^{Ar}$), 86.6 (CTf_2), 55.2 (OCH_3), 36.1 (CH_2-*allylic*), 29.3 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 13.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.68 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1607 (C=C), 1375, 1102 (O=S=O), 1193 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{18}O_5S_2F_6$ [*M*]$^{+}$: 480.0500; found: 480.0504. CCDC-1007421 contains the supplementary crystallographic data for compound **3c** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Cyclobutene 3d. From 60 mg (0.28 mmol) of alkyne **2d**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3d** (36 mg, 25%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 0.96 (t, 3H, *J* = 7.3 Hz, CH_3), 1.46 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.62 (t, 2H, *J* = 7.7 Hz, CH_2), 3.43 (s, 2H, CH_2-*allylic*), 7.75 (m, 2H, $2CH^{Ar}$), 8.29 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 161.5 [*C*=C-$(CH_2)_3CH_3$], 147.9 (C^{q}-NO_2), 135.5 (C^{q}), 130.1 [C=*C*-$(CH_2)_3CH_3$], 128.8 ($2CH^{Ar}$), 124.0 ($2CH^{Ar}$), 119.7 (q, J_{CF} = 331.1 Hz, $2CF_3$), 86.2 (CTf_2), 36.8 (CH_2-*allylic*), 29.8 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 13.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.44 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1641 (C=C), 1381, 1107 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{15}O_6NS_2F_6$ [*M*]$^{+}$: 495.0245; found: 495.0224.

Cyclobutene 3e. From 30 mg (0.21 mmol) of alkyne **2e**, and after chromatography of the residue using hexanes/diethyl ether (95:5) as eluent gave compound **3e** (39 mg, 41%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 0.52 (m, 1H,C*H*H), 0.77 (m, 1H,CH*H*), 0.91 (m, 1H,C*H*H), 1.07 (m, 1H,CH*H*), 1.99 (m, 1H, CH), 2.54 (d, 1H, *J* = 14.6 Hz, C*H*H-*allylic*), 3.26 (d, 1H, *J* = 14.6 Hz CH*H*-*allylic*), 7.50 (m, 3H, 3CH^{Ar}), 8.00 (m, 2H, 2CH^{Ar}); ^{13}C NMR (175 MHz, $CDCl_3$, 25 ^{o}C): δ = 161.7 (*C*=C-*cyclopropane*), 133.2 (CH^{Ar}), 130.3 (2CH^{Ar}), 129.0 (2CH^{Ar}), 127.7 (C^{q}), 127.4 (C=*C*-*cyclopropane*), 120.1 (q, J_{CF} = 330.6 Hz, CF_3), 119.8 (q, J_{CF} = 336.6 Hz, CF_3), 72.8 (CTf_2), 31.9 (CH_2-*allylic*), 9.8 (CH), 5.8 (CH_2), 1.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –71.80 and –77.79 (s, each 3F, CF_3); IR ($CHCl_3$): ν = 1598 (C=C), 1366, 1103 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{12}O_4S_2F_6$ [*M*]$^{+}$: 434.0081; found: 434.0078.

Cyclobutene 3f. From 30 mg (0.21 mmol) of alkyne **2f**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **3f** (40 mg, 51%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 0.50 (m, 1H,C*H*H), 0.76 (m, 1H,C*H*H), 0.87 (m, 1H,CH*H*), 1.03 (m, 1H,CH*H*), 1.98 (m, 1H,CH), 2.49 (d, 1H, *J* = 14.3 Hz, C*H*H-*allylic*), 3.21 (d, 1H, *J* = 14.3 Hz CH*H*-*allylic*), 3.89 (s, 3H, CH_3O), 6.98 (m, 2H, 2CH^{Ar}), 8.09 (m, 2H, 2CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 163.7 (C^{q}-OCH_3), 160.8 (*C*=C-*cyclopropane*), 133.2 (2CH^{Ar}), 122.1 (C=*C*-*cyclopropane*), 120.6 (C^{q}), 120.2 (q, J_{CF} = 330.8 Hz, CF_3), 120.0 (q, J_{CF} = 326.7 Hz, CF_3), 114.6 (2CH^{Ar}), 72.4 (CTf_2), 55.6 (CH_3O), 31.5 (CH_2-*allylic*), 10.0 (CH), 5.7 (CH_2), 1.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –71.82 and –78.09 (s, each 3F, CF_3); IR ($CHCl_3$): ν = 1603 (C=C), 1367, 1107 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{14}O_5S_2F_6$ [*M*]$^{+}$: 464.0187; found: 464.0183.

Cyclobutene 3g. From 50 mg (0.38 mmol) of alkyne **2g**, and after chromatography of the residue using hexanes/diethyl ether (9:1) as eluent gave compound **3g** (116 mg, 72%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.86 (s, 1H, OH), 3.52 (s, 2H, CH_2-*cyclobutene*), 4.66 (s, 2H, CH_2), 7.46 (m, 5H, 5CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 153.6 (*C*=C-CH_2), 132.5 (C=*C*-CH_2), 129.9 (CH^{Ar}), 129.1 (C^{q}), 128.8 (2CH^{Ar}), 127.9 (2CH^{Ar}), 119.8 (q, J_{CF} = 331.3 Hz, 2CF_3), 85.9 (CTf_2), 58.5 (CH_2OH), 35.2 (CH_2-*cyclobutene*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.46 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 3412 (OH), 1381, 1103 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}O_5S_2F_6$ [*M*]$^{+}$: 423.9874; found: 423.9872.

Cyclobutene 3h. From 40 mg (0.22 mmol) of alkyne **2h**, and after chromatography of the residue using hexanes/diethyl ether (9:1) as eluent gave compound **3h** (72 mg, 68%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.86 (s, 1H, OOH), 3.48 (s, 2H, CH_2-*cyclobutene*), 3.86 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 6.98 (m, 2H, 2CH^{Ar}), 7.53 (m, 2H, 2CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 161.4 (C^{q}-OCH_3), 141.3 (*C*=C-CH_2), 137.8 (C=*C*-CH_2), 129.9 (2CH^{Ar}), 120.8 (C^{q}), 119.7 (q, J_{CF} = 331.2 Hz, 2CF_3) 114.5 (2CH^{Ar}), 86.1 (CTf_2), 66.5 (CH_2OOH), 55.4 (OCH_3), 35.7 (CH_2-*cyclobutene*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.40 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1651 (C=C), 1383, 1104 (O=S=O), 1277 (C–O), 1209 (C–F), 840 (O–OH) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}O_7S_2F_6$ [*M*]$^{+}$: 469.9929; found: 469.9917.

Cyclobutene 3i. From 50 mg (0.30 mmol) of alkyne **2i**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3i** (102 mg, 74%) as a colorless solid; mp 52–54 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 0.97 (t, 3H, *J* = 7.2 Hz, CH_3), 1.42 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 2.60 (t, 2H, *J* = 7.5 Hz, CH_2), 3.39 (s, 2H, CH_2-*allylic*), 7.07 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 7.41 (d, 1H, *J* = 4.6 Hz, CH^{Ar}), 7.52 (d, 1H, *J* = 3.7 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 153.5 [*C*=C-$(CH_2)_3CH_3$], 130.9 [C=*C*-$(CH_2)_3CH_3$], 129.1 (CH^{Ar}), 127.7 (CH^{Ar}), 127.6 (CH^{Ar}), 125.1 (C^{q}), 119.8 (q, J_{CF} = 331.4 Hz, 2CF_3), 85.5 (CTf_2), 37.1 (CH_2-*allylic*), 29.6 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 13.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –71.08 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1383, 1107

(O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{14}O_4S_3F_6$ $[M]^+$: 455.9958; found: 455.9939.

Cyclobutene 3j. From 40 mg (0.22 mmol) of alkyne **2j**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **3j** (59 mg, 56%) as a colorless solid; mp 100–102 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 3.24 (s, 2H, CH_2), 6.51 (dd, 1H, *J* = 5.1, 3.7 Hz, CH^{Ar}), 6.67 (dd, 1H, *J* = 5.1, 1.1 Hz, CH^{Ar}), 6.96 (m, 3H, $3CH^{Ar}$), 7.16 (m, 2H, $2CH^{Ar}$), 7.63 (d, 1H, *J* = 2.9 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 149.8 (*C*=C-Thf), 131.4 (CH^{Ar}), 131.3 (CH^{Ar}), 130.9 (C=*C*-Ph), 130.8 (C^q), 128.9 ($2CH^{Ar}$), 128.4 (CH^{Ar}), 127.9 (CH^{Ar}), 127.6 ($2CH^{Ar}$), 123.0 (C^q), 120.4 (q, J_{CF} = 331.6 Hz, $2CF_3$), 87.3 (CTf_2), 35.3 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.89 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1381, 1105 (O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}O_4S_3F_6$ $[M]^+$: 475.96454; found: 475.96517.

Cyclobutene 3k. From 20 mg (0.21 mmol) of alkyne **2k**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3k** (36 mg, 75%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.88 (m, 1H, C*H*H), 2.02 (m, 2H, CH_2), 2.31 (m, 1H, CH*H*), 3.34 (d, 1H, *J* = 15.7 Hz, C*H*H-*allylic*), 3.48 (d, 1H, *J* = 15.7 Hz, CH*H*-*allylic*), 3.84 (s, 3H, OCH_3), 3.91 (m, 2H, CH_2), 4.90 (t, 2H, *J* = 7.2 Hz, CH), 6.93 (m, 2H, $2CH^{Ar}$), 7.50 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.5 (C^q-OCH_3), 153.4 (*C*=C-THF), 131.3 (C=*C*-THF), 129.7 ($2CH^{Ar}$), 121.8 (C^q), 119.8 (q, J_{CF} = 331.4 Hz, $2CF_3$), 114.1 ($2CH^{Ar}$), 85.8 (CTf_2), 74.1 (CH), 69.1 (CH_2), 55.3 (OCH_3), 34.4 (CH_2-*allylic*), 30.6 (CH_2), 26.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.59 and –70.75 (s, each 3F, CF_3); IR ($CHCl_3$): ν = 1608 (C=C), 1381, 1105 (O=S=O), 1024 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}O_6S_2F_6$ $[M]^+$: 494.0292; found: 494.0297.

Cyclobutene 3l. From 30 mg (0.1 mmol) of alkyne **2l**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **3l** (32 mg, 55%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.55 (s, 2H, CH_2-*cyclobutene*), 4.17 (s, 2H, C≡C-*C*H_2), 4.22 (s, 2H, CH_2Br), 7.54 (m, 4H, $4CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 148.9 (*C*=C-CH_2), 134.5 (*C*=C-CH_2), 132.4 ($2CH^{Ar}$), 128.7 (C^q), 128.0 ($2CH^{Ar}$), 124.5 (C^q), 119.7 (q, J_{CF} = 331.2 Hz, $2CF_3$), 87.0 (C≡*C*-CH_2), 85.8 (CTf_2), 85.5 (*C*≡C-CH_2), 36.3 (CH_2-*cyclobutene*), 23.0 (CH_2Br), 14.6 (C≡C-*C*H_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.34 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1603 (C=C), 1366, 1108 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}O_4S_2F_6Br_2$ $[M]^+$: 601.8291; found: 601.8307.

Cyclobutene 3m. From 40 mg (0.19 mmol) of alkyne **2m**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **3m** (50 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 1.39 (m, 2H, CH_2), 1.88 (t, 3H, *J* = 7.4 Hz, CH_3), 2.68 (s, 2H, CH_2-*allylic*), 2.98 (t, 2H, *J* = 6.4 Hz, CH_2), 6.89 (m, 3H, $3CH^{Ar}$), 7.31 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 165.3 (*C*=C-C≡C), 132.0 ($2CH^{Ar}$), 129.9 (CH^{Ar}), 128.7 ($2CH^{Ar}$), 121.1 (C^q), 120.3 (q, J_{CF} = 330.8 Hz, $2CF_3$), 115.2 (C=*C*-C≡C), 98.3 [C≡*C*-$(CH_2)_2CH_2Cl$], 86.4 (CTf_2), 77.9 [*C*≡C-$(CH_2)_2CH_2Cl$], 43.4 (CH_2), 36.3 (CH_2-*allylic*), 28.3 (CH_2), 28.0 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.39 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 2213 (C≡C), 1384, 1104 (O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{13}O_4S_2F_6Cl$ $[M]^+$: 493.9848; found: 493.98697.

Cyclobutene 3n. From 50 mg (0.16 mmol) of alkyne **2n**, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3n** (44 mg, 47%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.86 (m, 2H, CH_2), 2.53 (t, 2H, *J* = 6.8 Hz, CH_2), 2.75 (t, 2H, *J* = 7.7 Hz, CH_2), 3.37 (s, 2H, CH_2-*allylic*), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.83 (m, 2H, $2CH^{Ar}$), 6.88 (m, 2H, $2CH^{Ar}$), 7.31 (m, 2H, $2CH^{Ar}$), 7.55 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 160.3 (*C*^{q}-OCH_3), 159.3 (*C*^{q}-OCH_3), 153.7

[*C*=C-$(CH_2)_3$-], 132.9 ($2C^{Ar}H$), 132.7 [C=*C*-$(CH_2)_3$-], 129.5 ($2C^{Ar}H$), 122.2 (C^q), 119.8 (q, J_{CF} = 331.3 Hz, $2CF_3$), 115.5 (C^q), 114.1 ($2C^{Ar}H$), 113.9 ($2C^{Ar}H$), 86.7 (CTf_2), 86.6 (*C*≡C-PMP), 81.9 (C≡*C*-PMP), 55.3 (OCH_3), 55.2 (OCH_3), 36.1 (CH_2-a*llylic*), 28.5 (CH_2), 25.2 (CH_2), 19.0 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.63 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1605 (C=C), 1379, 1104 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{22}O_6S_2F_6$ $[M]^+$: 596.0762; found: 596.0767.

Cyclobutene 3o. From 50 mg (0.16 mmol) of alkyne **2n**, and after chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **3o** (122 mg, 86%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.81 (q, 2H, *J* = 7.3 Hz, CH_2), 2.62 (t, 4H, *J* = 7.3 Hz, $2CH_2$), 3.27 (s, 4H, $2CH_2$-*allylic*), 3.82 (s, 6H, $2OCH_3$), 6.88 (m, 4H, $4CH^{Ar}$), 7.44 (m, 4H, $4CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.5 ($2C^q$-OCH_3), 152.5 [$2C$=C-$(CH_2)_3$-], 133.5 [2C=*C*-$(CH_2)_3$-], 129.4 ($4C^{Ar}H$), 121.8 ($2C^q$), 119.8 (q, J_{CF} = 331.1 Hz, $4CF_3$), 114.1 ($4C^{Ar}H$), 86.5 ($2CTf_2$), 55.2 ($2OCH_3$), 35.8 ($2CH_2$-*allylic*), 28.6 ($2CH_2$), 22.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.55 (s, 12F, $4F_3$); IR ($CHCl_3$): ν = 1607 (C=C), 1378, 1103 (O=S=O), 1200 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{29}H_{24}O_{10}S_4F_{12}$ $[M]^+$: 888.0061; found: 888.0047.

Cyclobutene 3p. From 30 mg (0.22 mmol) of alkyne **2p**, and after chromatography of the residue using hexanes/diethyl ether (95:5) as eluent gave compound **3p** (53 mg, 57%) as a yellow solid; mp 58–60 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.46 (s, 2H, CH_2), 3.84 (s, 3H, CH_3O), 6.83 (s, 1H, CH), 6.93 (m, 2H, $2CH^{Ar}$), 7.63 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 161.1 (C^q-OCH_3), 139.3 (*C*=CH), 134.6 (C=*C*H), 128.0 ($2C^{Ar}H$), 121.6 (C^q), 119.8 (q, J_{CF} = 331.3 Hz, $2CF_3$), 114.2 ($2C^{Ar}H$), 87.3 (CTf_2), 55.3 (CH_3O), 35.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.85 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1607 (C=C), 1383, 1105 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}O_5S_2F_6$ $[M]^+$: 423.9874; found: 423.9875.

Cyclobutene [D]**-3p.** From 40 mg (0.30 mmol) of alkyne [D]-**2p**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound [D]-**3p** (82 mg, 65%) as a yellow solid; mp 50–52 ºC; ^1H NMR (300 MHz, C_6D_6, 25 ºC): δ = 2.87 (s, 2H, CH_2), 3.15 (s, 3H, CH_3O), 5.70 [s, 1H, CH (92% D)], 6.54 (m, 2H, $2CH^{Ar}$), 7.51 (m, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 161.5 (C^q-OCH_3), 139.1 (*C*=CD), 134.9 (t, J_{CD} = 27.2 Hz, C=*C*D), 128.3 ($2CH^{Ar}$ – *overlapped with the solvent signal*), 122.6 (C^q), 120.4 (q, J_{CF} = 331.4 Hz, $2CF_3$), 114.4 ($2CH^{Ar}$), 87.8 (CTf_2), 54.8 (CH_3O), 35.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –71.21 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1606 (C=C), 1385, 1104 (O=S=O), 1210 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_9DO_5S_2F_6$ $[M]^+$: 424.9937; found: 424.9955.

Cyclobutene 3q. From 50 mg (0.46 mmol) of alkyne **2q**, and after chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3q** (125 mg, 68%) as a colorless solid; mp 52–54 ºC; ^1H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 3.50 (s, 2H, CH_2), 6.72 (s, 1H, CH), 7.07 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 7.42 (d, 1H, *J* = 4.9 Hz, CH^{Ar}), 7.55 (d, 1H, *J* = 3.6 Hz, CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 135.2 (C=*C*H), 133.3 (*C*=CH), 131.4 (C^q), 129.8 (CH^{Ar}), 128.4 (CH^{Ar}), 128.2 (CH^{Ar}), 119.8 (q, J_{CF} = 331.2 Hz, $2CF_3$), 87.0 (CTf_2), 36.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.77 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1621 (C=C), 1384, 1105 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{10}H_6O_4S_3F_6$ $[M]^+$: 399.9332; found: 399.9344.

Cyclobutene 3r. From 50 mg (0.38 mmol) of alkyne **2r**, and after chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **3r** (158 mg, 58%) as a colorless oil; ^1H NMR (300 MHz, C_6D_6, 25 ºC): δ = 2.69 (s, 4H, $2CH_2$), 5.44 (t, 2H, *J* = 1.3 Hz, 2CH), 7.25 (s, 2H, $2CH^{Ar}$); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 139.3 (2C=*C*H),

133.7 (2*C*=CH), 131.9 (2C^{q}), 130.4 (2CH^{Ar}), 120.2 (q, J_{CF} = 331.2 Hz, 4CF_3), 87.3 (2CTf_2), 36.2 (2CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.99 (s, 12F, 4CF_3); IR ($CHCl_3$): ν = 1384, 1103 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_8O_8S_5F_{12}$ [*M*]$^+$: 715.86311; found: 715.86223.

Preparation of cyclobutene 3s and pyridine 4s. From 40 mg (0.39 mmol) of alkyne **2s**, and after chromatography of the residue using hexanes/diethyl ether (9:1) as eluent, 15 mg (32%) of the more polar compound **3s** and 35 mg (30%) of the less polar compound **4s** were obtained.

Cyclobutene 3s. Colorless solid; mp 39–40 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.50 (s, 2H, CH_2), 7.01 (s, 1H, CH), 7.43 (m, 3H, 3CH^{Ar}), 7.68 (m, 3H, 3CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 140.0 (*C*=CH), 137.7 (C=*C*H), 130.4 (CH^{Ar}), 128.9 (C^{q}), 128.8 (2CH^{Ar}), 126.3 (2CH^{Ar}), 119.8 (q, J_{CF} = 331.3 Hz, 2CF_3), 87.4 (CTf_2), 35.7 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.72 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1379, 1100 (O=S=O), 1194 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_8O_4S_2F_6$ [*M*]$^+$: 393.9768; found: 393.9778.

Pyridine 4s. Colorless solid; mp 68–70 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.02 (s, 3H, CH_3), 7.55 (m, 3H, 3CH^{Ar}), 7.85 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 8.14 (m, 2H, 2CH^{Ar}), 8.38 (d, 1H, *J* = 8.5 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.9 (*C*^{q}-CH_3), 161.2 (*C*^{q}-N), 142.0 (CH^{Ar}-*Piridina*), 136.7 (C^{q}-*Ph*), 131.2 (CH^{Ar}-*Ph*), 129.1 (2CH^{Ar}), 127.8 (2CH^{Ar}), 124.6 (C^{q}-Tf), 120.1 (q, J_{CF} = 326.3 Hz, CF_3), 118.1 (CH^{Ar}-*pyridine*), 24.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.26 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1377, 1126 (O=S=O), 1215 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}O_2NSF_3$ [*M*]$^+$: 301.0384; found: 301.0394.

Preparation of cyclobutene 3t and pyridine 4t. From 40 mg (0.31 mmol) of alkyne **2t**, and after chromatography of the residue using hexanes/diethyl ether (99:1) as eluent, 45 mg (35%) of the more polar compound **3t** and 31 mg (31%) of the less polar compound **4t** were obtained.

Cyclobutene 3t. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 3.14 (s, 1H, C≡CH), 3.50 (s, 2H, CH_2), 7.05 (s, 1H, CH), 7.40 (t, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.54 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.69 (t, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.76 (s, 1H, CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 139.5 (*C*=CH), 139.4 (C=*C*H), 134.3 (CH^{Ar}), 130.1 (CH^{Ar}), 129.5 (C^{q}), 129.4 (CH^{Ar}), 127.2 (CH^{Ar}), 123.4 (C^{q}), 120.2 (q, J_{CF} = 331.1 Hz, 2CF_3), 87.7 (CTf_2), 82.8 (*C*≡CH), 78.9 (C≡*C*H), 36.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.65 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 3301 (≡CH), 1382, 1101 (O=S=O), 1210 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_8O_4S_2F_6$ [*M*]$^+$: 417.9768; found: 417.9773.

Pyridine 4t. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 3.02 (s, 3H, CH_3), 3.17 (s, 1H, C≡CH), 7.51 (t, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.66 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.84 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 8.12 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 8.26 (s, H, CH^{Ar}), 8.39 (d, 1H, *J* = 8.4 Hz, CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 161.8 (*C*^{q}-CH_3), 161.3 (*C*^{q}-N), 142.2 (CH^{Ar}-*pyridine*), 137.0 (C^{q}), 134.5 (CH^{Ar}), 131.5 (CH^{Ar}), 129.2 (CH^{Ar}), 128.1 (CH^{Ar}), 125.1 (C^{q}-Tf), 123.2 (*C*^{q}-C≡CH), 120.0 (q, J_{CF} = 326.3 Hz, CF_3), 118.2 (CH^{Ar}-*pyridine*), 82.9 (*C*≡CH), 78.2 (C≡*C*H), 24.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.18 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1370, 1124 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{10}O_2NSF_3$ [*M*]$^+$: 325.0384; found: 325.0382.

Pyridine 4u. From 30 mg (0.20 mmol) of alkyne **2u**, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3u** (20 mg, 28%) as a

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ = 3.05 (s, 3H, CH_3), 7.94 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 8.31 (m, 2H, $2CH^{Ar}$), 8.40 (m, 2H, $2CH^{Ar}$), 8.47 (d, 1H, *J* = 8.4 Hz, CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ = 161.6 (C^{q}-CH_3), 160.2 (C^{q}-N), 149.4 (C^{q}-NO_2), 142.6 (CH^{Ar}-*pyridine*), 142.3(C^{q}-*Ph*), 128.8 ($2CH^{Ar}$), 126.3 (C^{q}-Tf), 124.2 ($2CH^{Ar}$), 119.9 (q, J_{CF} = 326.4 Hz, CF_3), 118.9 (CH^{Ar}-*pyridine*), 24.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –79.99 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1562, 1369 (NO_2), 1347, 1120 (O=S=O), 1197 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_9O_4N_2SF_3$ $[M]^{+}$: 346.0235; found: 346.0251.

Computational Details: All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs[24] at the dispersion corrected M06-2X[25]/6-31+(d) level. Reactants and products were characterized by frequency calculations,[26] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[27] Solvents effects were taken into account using the Polarizable Continuum Model (PCM)[28] in the geometry optimizations and frequency calculations (solvent = acetonitrile). This level is denoted PCM(acetonitrile)-M06-2X/6-31+G(d).

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V. CAPÍTULO 2

V.1. Regioselective Synthesis of Heteroatom-Functionalized Cyclobutene-triflones and Cyclobutenones

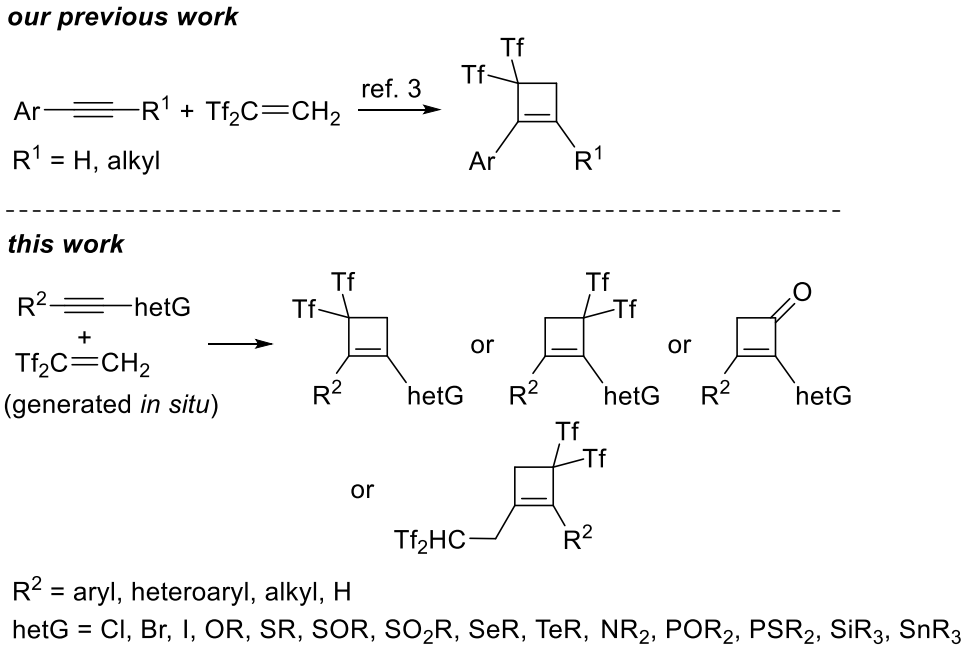
The controlled metal-free synthesis of a vast variety of heteroatom-containing cyclobutenetriflones [bis(trifluoromethylsulfonyl)cyclobutenes] and cyclobutenones has been developed starting from heteroatom-substituted alkynes and a pyridinium salt (a latent $Tf_2C{=}CH_2$ source). This powerful methodology, involving cyclization reactions, allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulfur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

Adv. Synth. Catal. **2017**, *359*, 2630

V.2. Article

V.2.1. Introduction

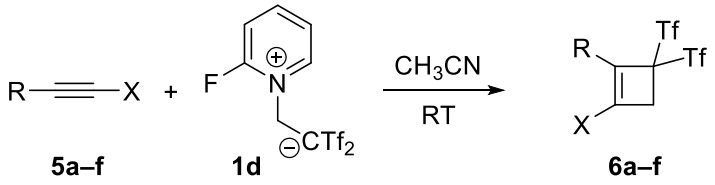
The importance of the synthesis of the cyclobutene core is ever increasing in relation to its presence in natural products and biologically active substances.[1] In addition to its biological importance, this strained carbocycle serves as versatile building block and has attracted considerable attention in organic synthesis.[2] One of the most challenging issues in synthesizing cyclobutenes is how to efficiently and selectivity introduce functionality into the four-membered carbocyclic skeleton. We have recently communicated the cyclization reaction of alkynes and $Tf_2C{=}CH_2$ to afford 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes, but this method was restricted so far to 1-aryl-2-alkyl(aryl)-substituted alkynes.[3] Due to the marked influence on the physical, chemical, and biological properties of small molecules imparted by the presence of heteroatoms, we envisaged the development of a mild method for the preparation of cyclobutene derivatives bearing an extra heteroatom directly linked to an sp2 carbon atom of the carbocycle (Scheme V.1). These heteroatom- substituted cyclobutene-triflones [bis(trifluoromethylsulfonyl) cyclobutenes or bis(triflyl)cyclobutenes][4,5] should bring together the new properties conferred by heteroatoms and the triflyl group with the exceptionally rich chemistry of cyclobutenes.

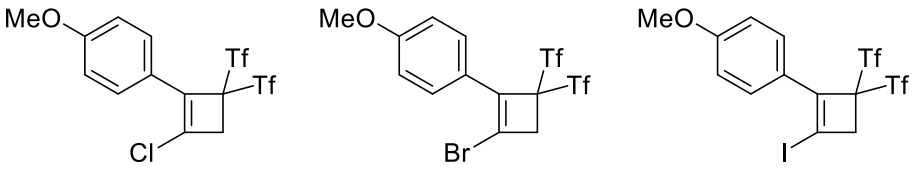


Scheme V.1. Metal-free room temperature synthesis of heteroatom-substituted cyclobutene-triflones or cyclobutenones.

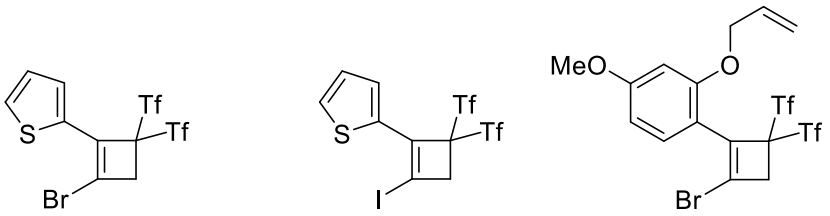
V.2.2. Results and discussion

To explore the effect of various heteroatomic substituentson cyclobutene-triflone formation, several differently functionalized alkynes were selected. 1-Chloroalkyne **5a** was chosen as model substrate to optimize suitable conditions for the reaction with pyridinium salt **1d**, a $Tf_2C{=}CH_2$ source. Zwitterion **1d** poorly soluble in apolar or halogenated solvents, which limited the optimization of the solvent parameter. Acetonitrile at room temperature was identified as the best choice for the reaction of 1-chloroalkyne **5a** with **1d**. Notably, the reaction of **5a** with **1d** led to bis(trifluoromethylsulfonyl)chlorocyclobutene **6a**, which was obtained in good yield (84%) as single regioisomer without the requirement of any catalyst (Scheme V.2).





6a (84%, 3 h) **6b** (92%, 3 h) **6c** (97%, 3 h)



6d (85%, 2 h) **6e** (96%, 2 h) **6f** (73%, 10 min)

Scheme V.2. Controlled preparation of bis(trifluoromethylsulfonyl) halocyclobutenes **6**.

Addition of H_2O may be beneficial by enhancing the solubility of the zwitterionic reagent **1d**. However, when the reaction was carried out in a mixture of

acetonitrile/water (1:1), chlorocyclobutene **6a** was obtained in decreased yield (70%). We further investigated the effect of different halogens on the cyclization as shown in Scheme V.2. Reaction of 1-bromo(iodo)alkynes **5b–f** with $Tf_2C{=}CH_2$ afforded cycloadducts **6b–f** as sole products in 73–97% yields. Electron-rich substituents accelerated the reaction progress, as exemplified with the formation of bromocyclobutene-triflone **6f** in just 10 min. The structure and regiochemistry of compound **6d** was unambiguously assigned through its X-ray crystallographic analysis (Figure V.1).[6]

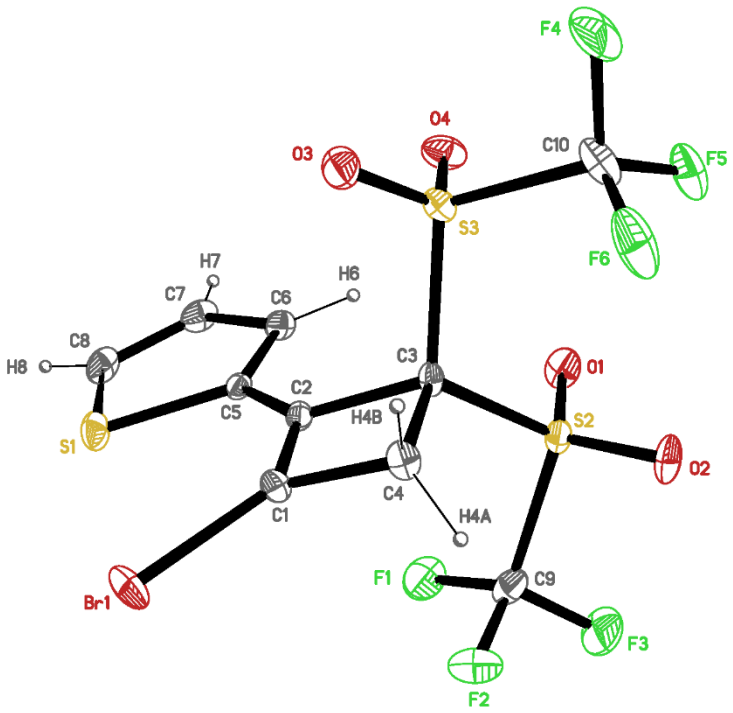
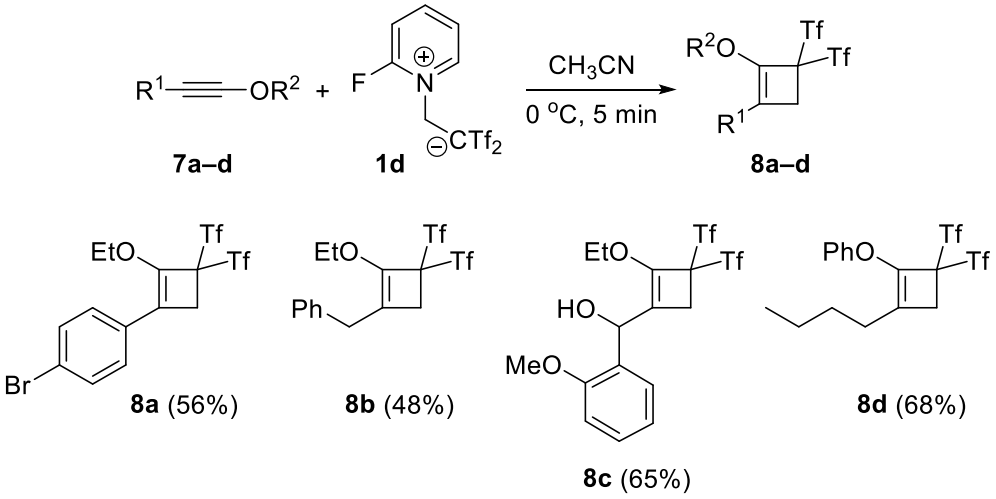


Figure V.1. ORTEP drawing of bis(trifluoromethylsulfonyl)-bromocyclobutene **6d**. Thermal ellipsoids shown at 50% probability.

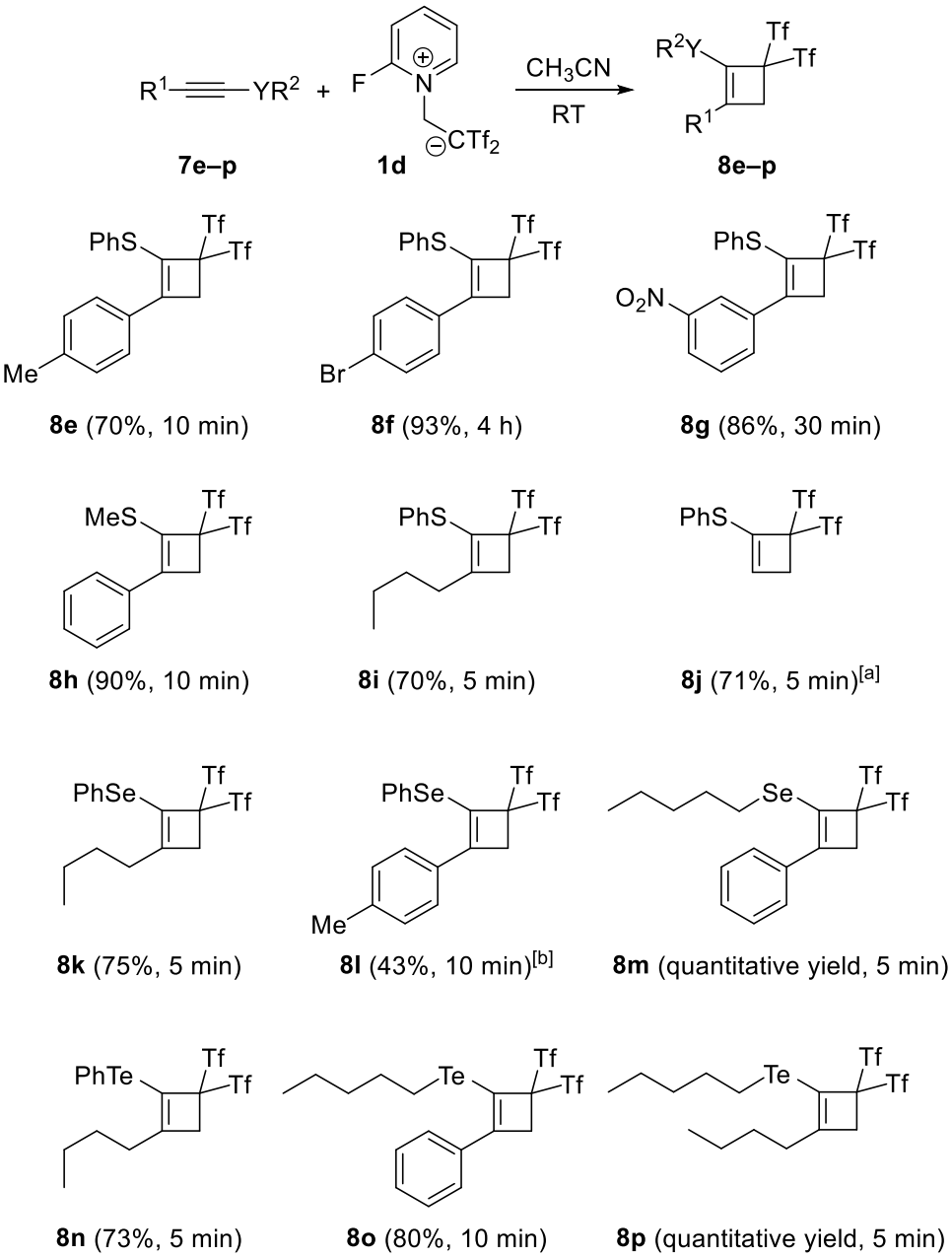
With the best halocyclobutene-triflone formation conditions identified, the scope of this transformation was then examined in alkynyl ethers, thioethers, selenoethers, and telluroethers **7**. Cyclization adducts **8a–d** could not be obtained at room temperature in reasonable yield because ynol ethers **7a–d** quickly reacted in contact with zwitterion **1d**, resulting in a complicated reaction. Fortunately, the reactions were more effective at 0ºC, and ynol ethers **7a–d** underwent smooth cyclization to afford cyclic enol ethers **8a–d**, in reasonable yields (Scheme V.3). Remarkably, the presence of OR groups instead halogens at the starting alkyne

reversed the product distribution completely, implying that the choice of substituents can control the regioselectivity of the reaction.



Scheme V.3. Controlled preparation of bis(trifluoromethylsulfonyl) enol ether cyclobutenes **8a–d.**

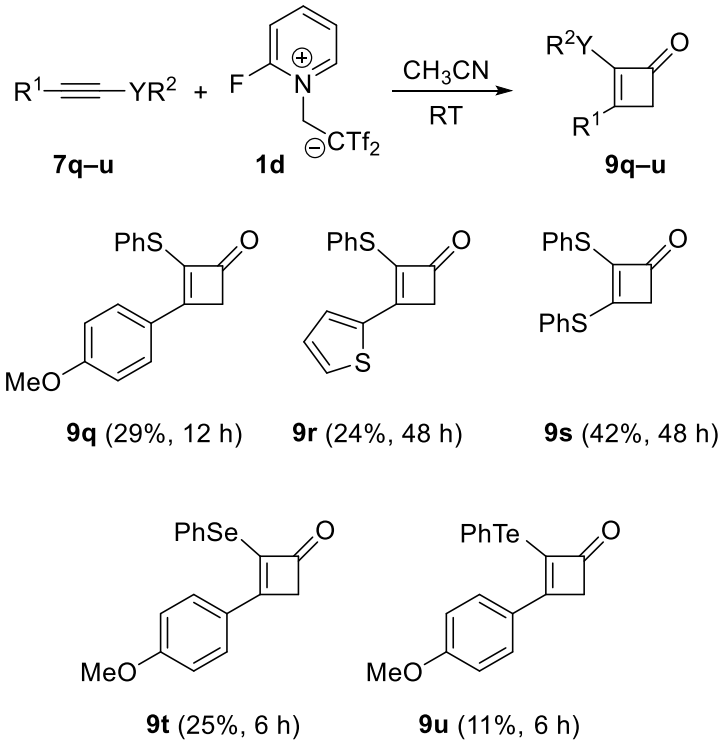
Organosulfur compounds occupy a special position in heteroatom-containing small molecules, both as bioactive compounds as well as synthetic intermediates.[7] We envisaged the preparation of cyclobutenetriflones bearing S-based groups starting from thia-alkynes. The proposed thia-cyclobutene-triflones present intringuing structures, the stability of which was initially in question given the supposed instability of chalcogen-substituted cyclobutene-triflones. Pleasingly, when using thia-alkynes **7e–j** and pyridinium salt **1d**, thia-cyclobutene-triflones **8e–j** were isolated in high yields (Scheme V.4), indicating the feasibility of this type of structures. In the case of sulfur-based substrates, the same level and sense of regioselectivity as in the oxygen derivatives was observed.



Scheme V.4. Controlled preparation of bis(trifluoromethylsulfonyl) chalcogen cyclobutenes **8**. [a] The reaction was carried out at 0ºC. [b] Partian decomposition during chromatographic purification.

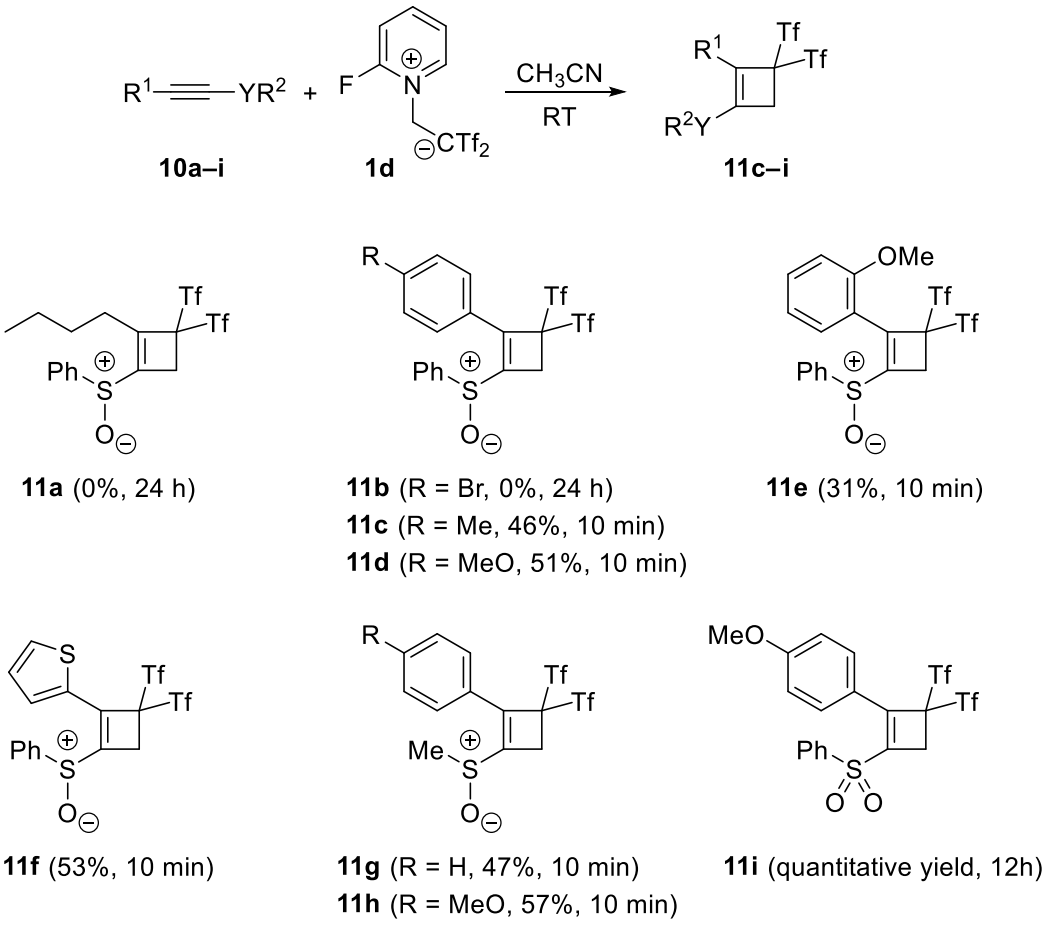
Cyclization precursors **7k–p** bearing Se and Te containing carbon chains were prepared. The standard cyclobutene formation conditions were then applied across this range of substrates. Alkynes **7k–p** efficiently formed the desired polyfunctionalized four-membered rings **8k–p**,[8] but the cyclization proved capricious for Se derivative **8l** due to partial degradation of the final material under the

chromatographic purification conditions (Scheme V.4). Interestingly, in all cases the product exhibited the same regiocontrol as the oxygen and sulfur derivatives. Chalcogen substrates **7q–u**, containing an additional electron-rich substituent at the other alkyne side, worked under the standard conditions to afford unexpected cyclobutene derivatives along with unidentified by-products. Cyclobutenones **9q–u** can be accessed from this type of substrates albeit with a lower yield (Scheme V.5).



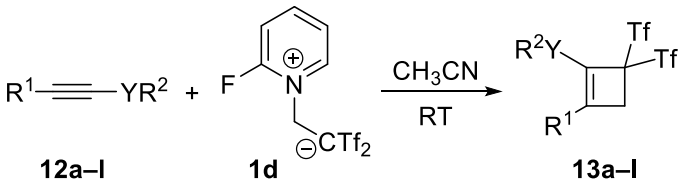
Scheme V.5. Preparation of bis(trifluoromethylsulfonyl)chalcogen cyclobutenones **9**.

The influence of different sulfur oxidation states on the reactivity was also tested. In addition to thia-alkynes **7e–j** we were interested in examining sulfinylalkynes **10a–h** and sulfonylalkyne **10i**. Firstly, the electronic effect on the S-substituent was investigated and the result showed that substrates bearing aliphatic substituents **10a** or deactivated benzene rings **10b** did not afford the desired cyclobutenes. By contrast, neutral or electron-rich aromatic substituents can be tolerated to provide sulfinylcyclobutenes **11c–h** and sulfonylcyclobutene **11i** (Scheme V.6).

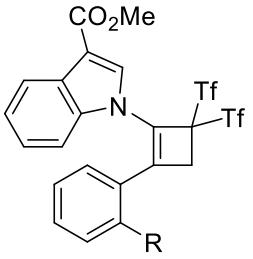


Scheme V.6. Controlled preparation of bis(trifluoromethylsulfonyl) sulfinylcyclobutenes **11d–h** and sulfonylcyclobutene **11i**.

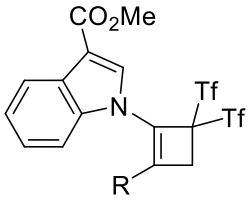
Notably, a regiochemistry reversal was observed on going from sulfur with oxidation number −2 such as in alkynes **7e–j** to sulphur with oxidation numbers +4 (alkynes **10c–h**) and +6 (alkyne **10i**). The effect of an amino group in the four-membered ring formation reaction was investigated with the use of indole-based ynamine derivatives **12a–l**. As in the case of OR, SR, SeR, and TeR substituents (Scheme V.3 - Scheme V.5), the regioselectivity reversal is dictated by the heteroatom. Ynamines **12a–l** afforded the corresponding cyclobutenes **13a–l** as the sole products in fair yields (Scheme V.7).



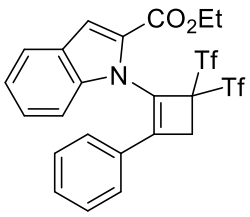
12a–l **1d** **13a–l**



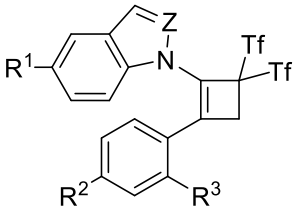
13a R = H (94%, 4 h)
13b R = MeO (33%, 3 h)



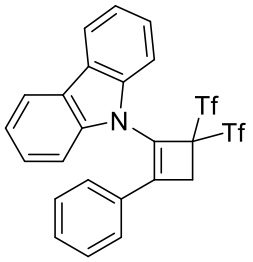
13c R = H (67%, 1 min)[a]
13d R = 2-thienyl (29%, 1 h)
13e R = 3-$MeOC_6H_4$ (95%, 2 h)
13f R = 3-$NO_2C_6H_4$ (82%, 5 h)
13g R = *n*-Bu (84%, 5 min)



13h (quantitative yield, 1 h)



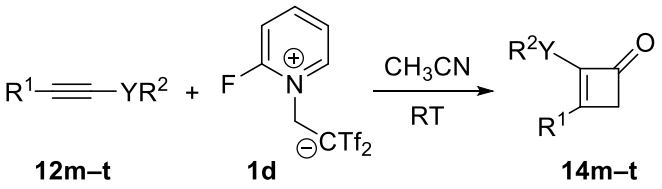
13i R^1 = H, R^2 = H, R^3 = H, Z = N (quantitative yield, 3 h)
13j R^1 = H, R^2 = H, R^3 = MeO, Z = N (40%, 1 h)
13k R^1 = Br, R^2 = Br, R^3 = H, Z = CH (72%, 30 min)



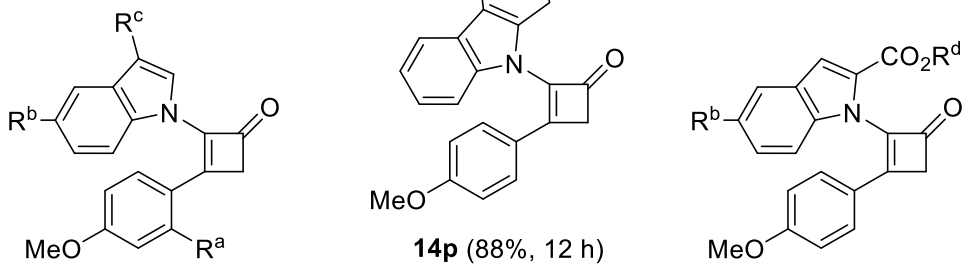
13l (88%, 1 min)

Scheme V.7. Controlled preparation of bis(trifluoromethylsulfonyl)indolylcyclobutenes **13a–l**. [a] The reaction was carried at 0ºC.

These examples also indicated that ynamines **12a**, **12h**, and **12i** bearing the simple phenyl ring at N-1 are the best starting materials, furnishing the highest yields (quantitative or almost quantitative yields) of the appropriate cyclobutenes. Unexpectedly, the results in Scheme V.8 show, in all instances, that ynamines **12m–t** having electronrich 4-$MeOC_6H_4$ groups furnished exclusively cyclobutenones **14m–t**.[9,10] Cyclobutenone formation is spontaneous under the reaction conditions, but it may be facilitated by the addition of water (2 equiv.) and K_2CO_3 (2 equiv.) during the work-up.



12m–t **1d** **14m–t**



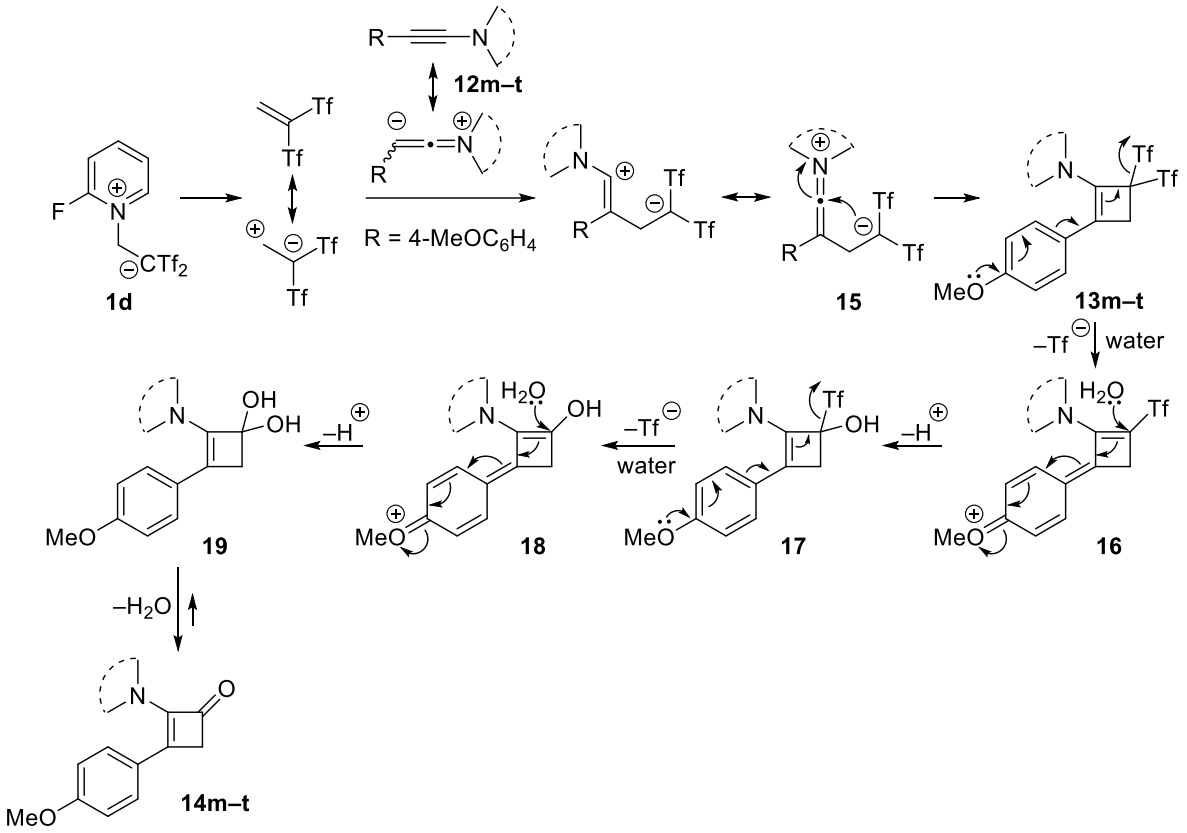
14p (88%, 12 h)

14m R^a = H, R^b = H, R^c = CO_2Me (86%, 12 h)
14n R^a = MeO, R^b = H, R^c = CO_2Me (23%, 12 h)[a]
14o R^a = H, R^b = Br, R^c = H (42%, 12 h)

14q R^b = H, R^d = Et (53%, 12 h)
14r R^b = Me, R^d = Et (45%, 12 h)
14s R^b = Cl, R^d = Et (51%, 12 h)
14t R^b = H, R^d = Ph (41%, 72 h)

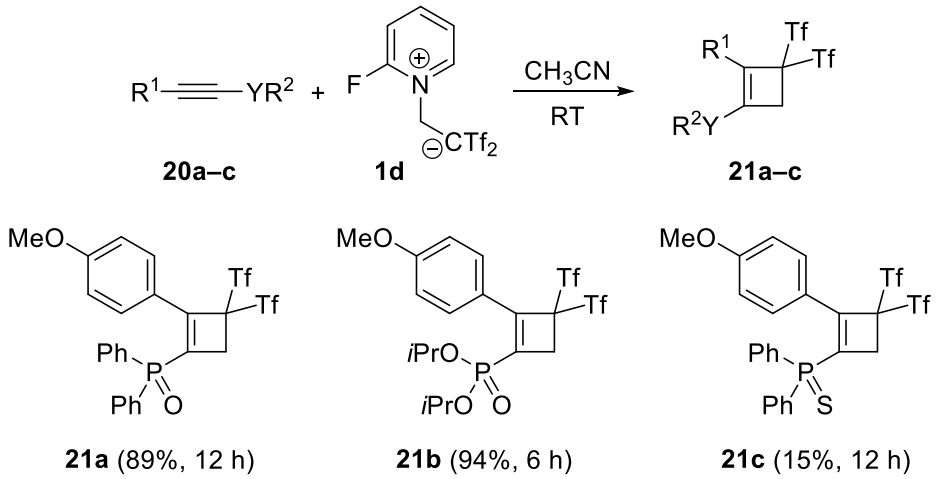
Scheme V.8. Controlled preparation of bis(trifluoromethylsulfonyl) indolylcyclobutenones **14m–t**. [a] Messy reaction.

As shown in Scheme V.9, the mechanism for the cyclobutenone formation involves two main processes, namely, cyclobutene ring construction and hydrolysis. The proposal for the first process (formation of **13m–t**) is based on our previous DFT studies of 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes,[5] but now the regioselectivity is dictated by the electronic effects of the heterocyclic amine. Adventitious water in the reaction medium is required for the double trifluoro(hydrosulfonyl)methane (TfH) elimination, giving rise to hydrates **19**. This two-fold water addition is assisted by the resonance effect of the 4-methoxy substituent in the 4-methoxyphenyl group. Finally, dehydration occurs in adducts **19** to afford cyclobutenones **14m–t**.



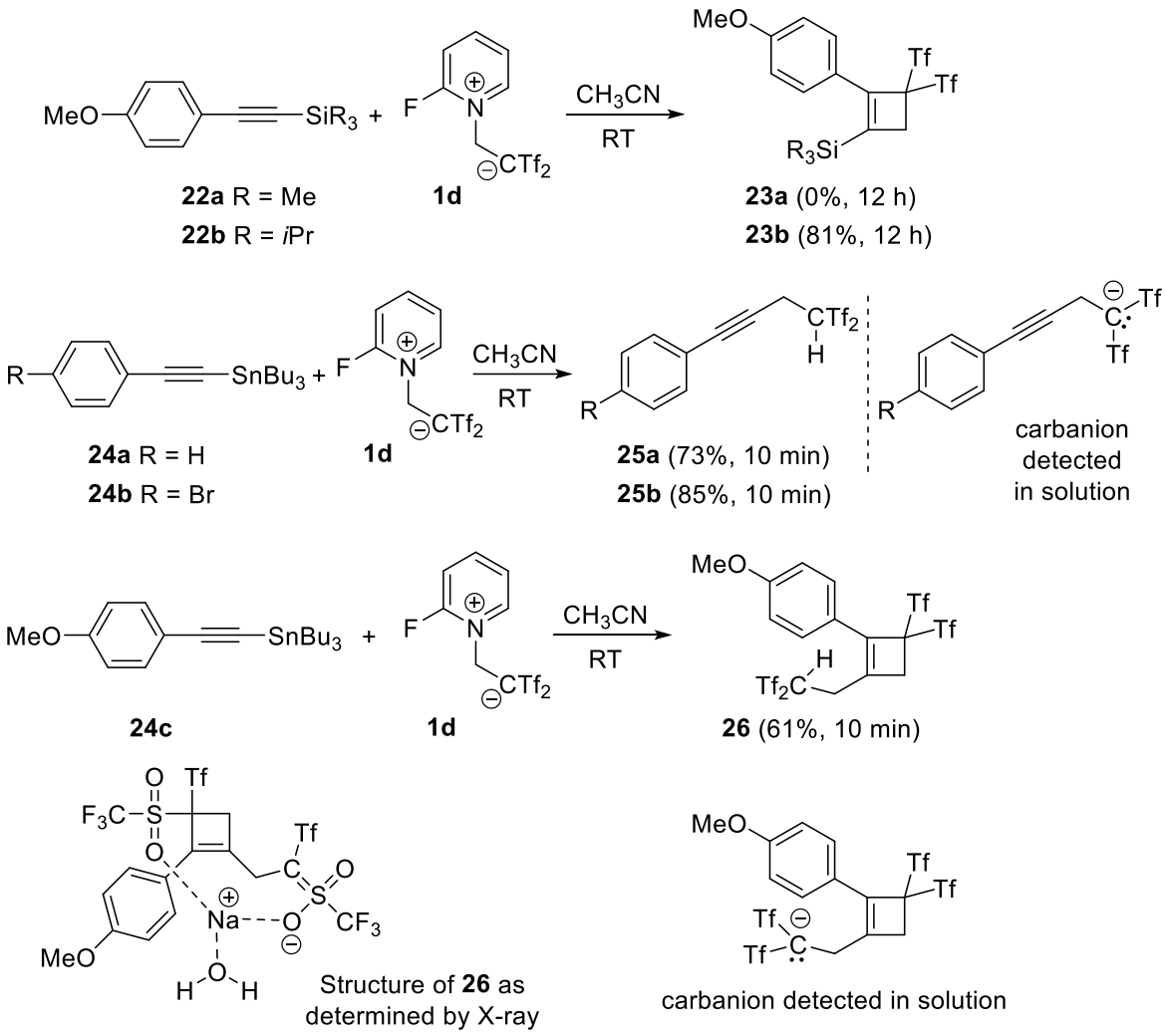
Scheme V.9. Rationalization for the formation of cyclobutenones **14**.

We decided to examine phosphorus-substituted alkynes **20** as precursors of functionalized cyclobutenes (Scheme V.10).[11] Screening of precursors **20** revealed that phosphine oxides **20a** and **20b** afforded phosphorylcyclobutenes **21a** and **21b** in excellent yields under the usual mild conditions. However, despite the fact that apparently thiophosphine oxide **20c** is a suitable substrate for the reaction, it produced the S=P(Ph)$_2$-substituted cyclobutene **21c** in just 15% yield.



Scheme V.10. Controlled preparation of bis(trifluoromethylsulfonyl) phosphorylcyclobutenes **21a–c**.

Taking into account the rich chemistry of organosilicon and organotin derivatives, we also became interested in the cyclobutenylation of trialkyl(ethynyl)silanes and trialkyl(ethynyl)stannanes by pyridinium salt **1d** as cyclization reagent. If successful, this reaction could afford carbon(sp^2)-linked trialkylsilyl- and trialkylstannylcyclobutenes. The formation of the expected TMS-cyclobutene **23a** was observed by TLC, but it could not be isolated for synthetic purposes. We were pleased to observe that the reaction of the TIPS alkyne **22b** afforded the corresponding TIPS-cyclobutene **23b** in high yield (Scheme V.11). An unexpected product was obtained starting from Bu_3Sn-alkyne **24a**, the identity of which was assigned as **25a** and resulted from the transformation of the Bu_3Sn group rather than the alkyne moiety. A similar behaviour was detected in the conversion of organotin derivative **24b** into adduct **25b**. Interestingly, stirring alkynylstannane **24c** at room temperature in acetonitrile with zwitterion **1d** led to the formation of tetra(trifluoromethylsulfonyl)cyclobutene **26**, in 61% isolated yield in just 10 min (Scheme V.11).



Scheme V.11. Controlled preparation of bis(trifluoromethylsulfonyl)silacyclobutene **23b** and triflone carbanions **25a**, **25b** and **26**.

Noticeably, compounds **25a**, **25b**, and **26** are carbon acids which in solution easily dissociate the acidic hydrogen and give rise to stable carbanions.[12] When the ^{1}H NMR spectra of **25a**, **25b**, and **26** were reorded, the signals for the hydrogen atoms of the Tf_2CH group could not be detected. Further supporting structural evidence was obtained through the X-ray crystallographic analysis of adduct **26** (Figure V.2).[13]

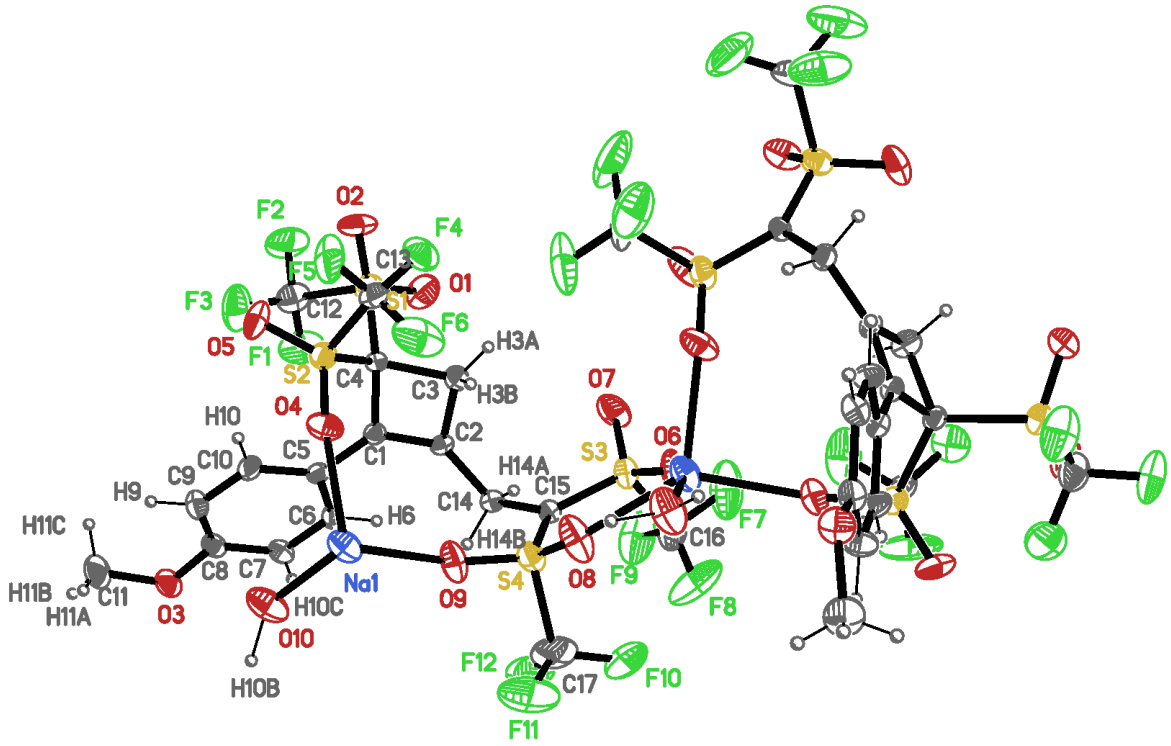
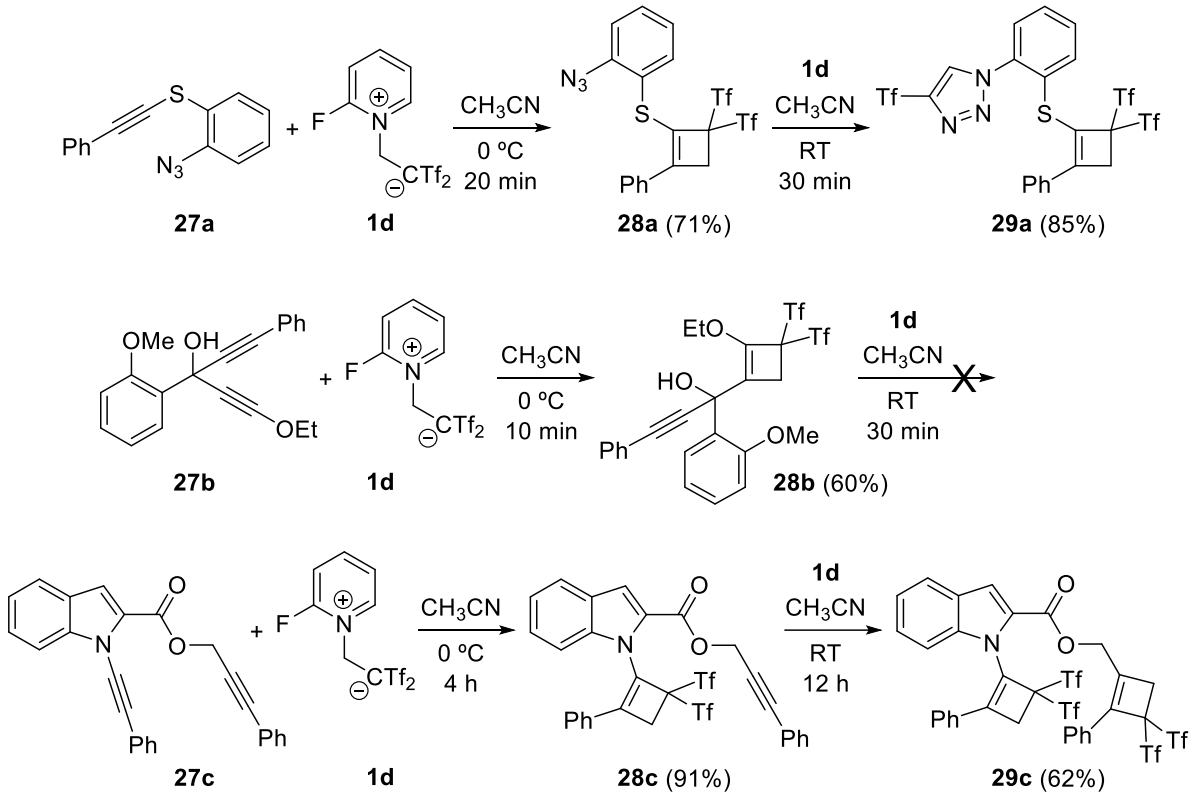


Figure V.2. ORTEP drawing of tetra(trifluoromethylsulfonyl)-cyclobutene **26**. Thermal ellipsoids shown at 50% probability.

To evaluate the goal of chemoselectivity, several functionalized heteroatom-containing alkynes **27a–c** were reacted under the above standard reaction conditions. Every single reaction reached full conversion to selectively afford cyclobutenes **28a–c**, in which monocyclization towards the heteroatom-substituted alkyne was favoured. Bis-functionalization of the remaining alkyne or azide functionality was achieved after the addition of a second equivalent of zwitterion **1d**, suggesting that the exquisite selectivity arises from the increased reactivity imparted by the heteroatom (Scheme V.12).



Scheme V.12. Chemoselective reaction of heteroatom-containing alkynes **27**.

V.2.3. Conclusion

In summary, we have developed a new metal-free synthesis of a vast variety of heteroatom-containing cyclobutene-triflones and cyclobutenones from the reaction of heteroatom-substituted alkynes with a pyridinium salt as a $Tf_2C{=}CH_2$ source. This powerful methodology, involving cyclization, allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulfur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

V.3. Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or acetone-d_6 (^{1}H, 2.05 ppm; ^{13}C, 206.3 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm), or DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. Column chromatography was carried out using silica gel 60, 0.04-0.06 mm, for flash chromatography (230-400 mesh ASTM) provided by Scharlau. All commercially available compounds were used without further purification.

General procedure for the uncatalyzed reaction of heteroatom-substituted alkynes and pyridinium salt 1d. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.2 mmol) was added at room temperature (or 0 ^{o}C) to a solution of the appropriate heteroatom-substituted alkyne **5a–f, 7a–u, 10a–i, 12a–l, 20a–c, 22a, 22b, 24a–c, 27a–c, 28a–c** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **6a–f, 8a–p, 9q–u, 11c–i, 13a–l, 21a–c, 23b, 25a, 25b, 26c, 28a–c, 29a, 29c** follow.

Bis(trifluoromethylsulfonyl)chlorocyclobutene 6a. From 33 mg (0.19 mmol) of alkyne **5a**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6a** (74 mg, 84%) as a colorless solid; mp 75–77 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.85 (m, 2H, $2CH^{Ar}$), 6.97 (m, 2H, $2CH^{Ar}$), 3.85 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 161.2 ($C^{Ar\text{-}q}$-OCH_3), 133.8 (*C*=C-Cl), 130.9 (C=*C*-Cl), 129.3 ($2CH^{Ar}$), 120.1 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 114.2 ($2CH^{Ar}$), 85.5 (CTf_2), 55.3 (OCH_3), 41.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.85 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1606 (C=C), 1386, 1100 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}ClF_6NO_5S_2$ $[M + NH_4]^+$: 475.9822; found: 475.9831.

Bis(trifluoromethylsulfonyl)bromocyclobutene 6b. From 24 mg (0.11 mmol) of alkyne **5b**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6b** (94 mg, 92%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.89 (m, 2H, $2CH^{Ar}$), 6.97 (m, 2H, $2CH^{Ar}$), 3.86 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 161.4 ($C^{Ar\text{-}q}$-OCH_3), 136.9 (*C*=C-Br), 129.1 ($2CH^{Ar}$), 120.4 ($C^{Ar\text{-}q}$), 120.2 (C=*C*-Br), 119.7 (q, J_{CF} = 331.5 Hz, $2CF_3$), 114.2 ($2CH^{Ar}$), 87.3 (CTf_2), 55.4 (CH_3O), 41.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.73 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1604 (C=C), 1384, 1101 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}BrF_6NO_5S_2$ $[M + NH_4]^+$: 519.9317; found: 519.9298.

Bis(trifluoromethylsulfonyl)iodocyclobutene 6c. From 43 mg (0.16 mmol) of alkyne **5c**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6c** (153 mg, 97%) as a pale yellow solid; mp 83–85 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.91 (m, 2H, $2CH^{Ar}$), 6.98 (m, 2H, $2CH^{Ar}$), 3.86 (s, 3H, OCH_3),

3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.5 ($C^{Ar\text{-}q}$-OCH_3), 142.4 (*C*=C-I), 128.7 ($2CH^{Ar}$), 121.2 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.5 Hz, $2CF_3$), 114.1 ($2CH^{Ar}$), 93.7 (C=*C*-I), 90.0 (CTf_2), 55.4 (CH_3O), 42.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.61 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1608 (C=C), 1384, 1103 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}IF_6NO_5S_2$ [*M* + NH_4]$^+$: 567.9179; found: 567.9177.

Bis(trifluoromethylsulfonyl)bromocyclobutene 6d. From 20 mg (0.106 mmol) of alkyne **5d**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6d** (43 mg, 85%) as a colorless solid; mp 95–97 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.72 (d, 1H, *J* = 3.7, CH^{Ar}), 7.56 (dd, 1H, *J* = 5.0, 0.8, CH^{Ar}), 7.12 (dd, 1H, *J* = 5.0, 3.9, CH^{Ar}), 3.76 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 131.8 (*C*=C-Br), 131.0 (CH^{Ar}), 129.5 (CH^{Ar}), 129.2 ($C^{Ar\text{-}q}$), 127.7 (CH^{Ar}), 119.7 (q, J_{CF} = 331.4 Hz, $2CF_3$), 119.5 (C=*C*-Br), 86.4 (CTf_2), 42.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.88 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1632 (C=C), 1389, 1104 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{10}H_9BrF_6NO_4S_3$ [*M* + NH_4]$^+$: 495.8776; found: 495.8781. 6. CCDC 1060047 contains the supplementary crystallographic data for compound **6d** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Bis(trifluoromethylsulfonyl)iodocyclobutene 6e. From 21 mg (0.089 mmol) of alkyne **5e**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **6e** (45 mg, 96%) as a colorless solid; mp 88–90 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.76 (d, 1H, *J* = 3.6, CH^{Ar}), 7.54 (dd, 1H, *J* = 5.0, 0.8, CH^{Ar}), 7.13 (dd, 1H, *J* = 5.0, 3.9, CH^{Ar}), 3.74 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 137.7 (*C*=C-I), 131.4 (CH^{Ar}), 130.2 ($C^{Ar\text{-}q}$), 128.9 (CH^{Ar}), 127.7 (CH^{Ar}), 119.7 (q, J_{CF} = 331.6 Hz, $2CF_3$), 92.7 (C=*C*-I), 89.0 (CTf_2), 43.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.85 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1613 (C=C), 1386, 1104 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{10}H_9IF_6NO_4S_3$ [*M* + NH_4]$^+$: 543.8637; found: 543.8671.

Bis(trifluoromethylsulfonyl)bromocyclobutene 6f. From 39 mg (0.146 mmol) of alkyne **5f**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **6f** (58 mg, 73%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.47 (d, 1H, *J* = 8.6, CH^{Ar}), 6.52 (dd, 1H, *J* = 8.6, 2.4, CH^{Ar}), 6.46 (d, 1H, *J* = 2.3, CH^{Ar}), 6.04 (m, 1H, C*H*=CH_2), 5.40 (ddd, 1H, *J* = 17.3, 3.1, 1.6 Hz, CH=CH*H*), 5.29 (ddd, 1H, *J* = 10.6, 2.8, 1.4 Hz, 1H, CH=C*H*H), 4.63 (dt, 2H, *J* = 5.2, 1.5 Hz, CH_2-*allyl*), 3.83 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2-*cyclobutenyl*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.8 ($C^{Ar\text{-}q}$-OCH_3), 157.8 ($C^{Ar\text{-}q}$-OCH_2), 136.6 (*C*=C-Br), 132.8 (*C*H=CH_2), 131.2 (CH^{Ar}), 127.6 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.6 Hz, $2CF_3$), 117.7 (CH=*C*H_2), 110.0 (C=*C*-Br), 104.9 (CH^{Ar}), 99.5 (CH^{Ar}), 89.3 (CTf_2), 69.1 (OCH_2), 55.4 (OCH_3), 40.6 (CH_2- *cyclobutenyl*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –69.86 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1607 (C=C), 1385, 1104 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}BrF_6NO_6S_2$ [*M* + NH_4]$^+$: 575.9579; found: 577.9559.

Bis(trifluoromethylsulfonyl)alkoxycyclobutene 8a. From 25 mg (0.11 mmol) of alkyne **7a**, and after flash chromatography of the residue using hexanes/triethylamine (98:2) as eluent gave compound **8a** (32 mg, 56%) as a colorless oil; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.12 (m, 2H, $2CH^{Ar}$), 6.58 (m, 2H, $2CH^{Ar}$), 3.74 (q, 2H, *J* = 7.0 Hz, OCH_2), 2.73 (s, 2H, CH_2), 0.86 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 136.0 (C=*C*-O), 132.1 ($2CH^{Ar}$), 129.0 ($2CH^{Ar}$), 128.9 ($C^{Ar\text{-}q}$), 128.5 ($C^{Ar\text{-}q}$), 124.2 (*C*=C-O), 120.4 (q, J_{CF} = 330.9 Hz, $2CF_3$), 88.7 (CTf_2), 69.7 (OCH_2), 28.7 (CH_2), 14.6 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.83 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1679 (C=C), 1382, 1105 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}BrF_6O_5S_2Na$ [*M* + Na]$^+$: 538.9028; found: 538.8996.

Bis(trifluoromethylsulfonyl)alkoxycyclobutene 8b. From 15 mg (0.09 mmol) of alkyne **7b**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **8b** (20 mg, 48%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.12 (m, 2H, 2CH^{Ar}), 7.01 (m, 3H, 3CH^{Ar}), 3.49 (q, 2H, *J* = 7.0 Hz, OCH_2), 2.99 (s, 2H, CH_2-*cyclobutenyl*), 2.42 (s, 2H, CH_2), 0.79 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 137.0 (C=*C*-O), 135.6 (C$^{Ar\text{-}q}$), 129.2 (2CH^{Ar}), 128.6 (2CH^{Ar}), 127.4 (CH^{Ar}), 123.6 (*C*=C-O), 120.2 (q, J_{CF} = 330.6 Hz, $2CF_3$), 86.7 (CTf_2), 67.8 (OCH_2), 33.8 (CH_2), 29.2 (CH_2-*cyclobutenyl*), 14.3 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –71.12 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1695 (C=C), 1381, 1103 (O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{18}F_6NO_5S_2$ [*M* + NH_4]$^{+}$: 470.0525; found: 470.0516.

Bis(trifluoromethylsulfonyl)alkoxycyclobutene 8c. From 20 mg (0.09 mmol) of alkyne **7c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **8c** (31 mg, 65%) as a pale orange oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ^{o}C): δ = 7.28 (dd, 1H, *J* = 7.5, 1.5 Hz, CH^{Ar}), 7.03 (td, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 6.83 (td, 1H, *J* = 7.5, 0.7 Hz, CH^{Ar}), 6.41 (d, 1H, *J* = 8.2 Hz, CH^{Ar}), 5.38 (s, 1H, C*H*OH), 3.38 (m, 2H, OCH_2), 3.19 (s, 3H, OCH_3), 2.81 (d, 1H, *J* = 12.2 Hz, C*H*H), 2.58 (d, 1H, *J* = 12.2 Hz, CH*H*), 2.27 (br s, 1H, OH), 0.89 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 ^{o}C): δ = 156.5 (C$^{Ar\text{-}q}$-OMe), 136.1 (C=*C*-O), 129.7 (CH^{Ar}), 127.7 (C$^{Ar\text{-}q}$), 127.3 (CH^{Ar}), 126.0 (*C*=C-O), 121.2 (CH^{Ar}), 120.3 (q, J_{CF} = 330.7 Hz, CF_3), 120.2 (q, J_{CF} = 330.8 Hz, CF_3), 110.7 (CH^{Ar}), 86.5 (CTf_2), 68.8 (OCH_2), 66.0 (CHOH), 54.7 (OCH_3), 28.3 (CH_2), 14.4 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –71.12 (s, 3F, CF_3), –71.34 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3422 (OH), 1691 (C=C), 1383, 1104 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{16}F_6NaO_7S_2$ [*M* + Na]$^{+}$: 521.0134; found: 521.0133.

Bis(trifluoromethylsulfonyl)phenoxycyclobutene 8d. From 20 mg (0.11 mmol) of alkyne **7d**, and after flash chromatography of the residue using hexanes/toluene (9:1→8:2) as eluent gave compound **8d** (36 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.40 (m, 2H, 2CH^{Ar}), 7.22 (m, 3H, 3CH^{Ar}), 2.98 (s, 2H, CH_2-*cyclobutenyl*), 1.77 (t, 3H, *J* = 7.2 Hz, CH_2), 1.24 (m, 4H, $2CH_2$), 0.79 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 154.1 (C$^{Ar\text{-}q}$-O), 133.7 (C=*C*-O), 132.5 (*C*=C-O), 129.9 (2CH^{Ar}), 125.6 (CH^{Ar}), 119.7 (q, J_{CF} = 330.5 Hz, $2CF_3$), 119.0 (2CH^{Ar}), 86.8 (CTf_2), 30.0 (CH_2-*cyclobutenyl*), 27.8 (CH_2), 27.0 (CH_2), 22.1 (CH_2), 13.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.91 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1695 (C=C), 1383, 1106 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{20}F_6NO_5S_2$ [*M* + NH_4]$^{+}$: 484.0682; found: 484.0671.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8e. From 33 mg (0.15 mmol) of alkyne **7e**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8e** (53 mg, 70%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.33 (m, 2H, 2CH^{Ar}), 7.15 (m, 2H, 2CH^{Ar}), 6.86 (m, 2H, 2CH^{Ar}), 6.77 (m, 1H, 1CH^{Ar}), 6.69 (m, 2H, 2CH^{Ar}), 3.31 (s, 2H, CH_2), 1.91 (s, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 161.7 (C=*C*-S), 143.1 (C$^{Ar\text{-}q}$), 131.2 (*C*$^{Ar\text{-}q}$), 129.5 (4CH^{Ar}), 129.2 (2CH^{Ar}), 128.5 (2CH^{Ar}), 127.6 (CH^{Ar}), 127.5 (C$^{Ar\text{-}q}$), 120.4 (q, J_{CF} = 331.3 Hz, $2CF_3$), 118.2 (*C*=C-S), 89.6 (CTf_2), 35.0 (CH_2), 21.4 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –70.39 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1604 (C=C), 1381, 1106 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}F_6NO_4S_3$ [*M* + NH_4]$^{+}$: 534.0297; found: 534.0283.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8f. From 30 mg (0.103 mmol) of alkyne **7f**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8f** (56 mg, 93%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.25 (m, 2H, 2CH^{Ar}), 6.96 (m, 2H, 2CH^{Ar}), 6.79 (m, 5H, 5CH^{Ar}), 3.17 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 159.0 (C=*C*-S), 131.9 (2CH^{Ar}), 130.3 (*C*$^{Ar\text{-}q}$), 129.7 (2CH^{Ar}), 129.6 (2CH^{Ar}), 129.5 (2CH^{Ar}), 128.6 (C$^{Ar\text{-}q}$), 128.0 (CH^{Ar}), 126.9 (C$^{Ar\text{-}q}$), 120.3 (q, J_{CF}

= 331.1 Hz, $2CF_3$), 121.0 (*C*=C-S), 89.2 (CTf_2), 34.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.29 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1599 (C=C), 1383, 1106 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{15}BrF_6NO_4S_3$ [*M* + NH_4]$^+$: 597.9245; found: 597.9231.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8g. From 10 mg (0.039 mmol) of alkyne **7g**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **8g** (18 mg, 86%) as a colorless solid; mp 121–123 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): d = 8.19 (m, 1H, CH^{Ar}), 8.10 (t, 1H, *J* = 1.9 Hz, CH^{Ar}), 7.64 (m, 1H, CH^{Ar}), 7.48 (m, 3H, $3CH^{Ar}$), 7.21 (m, 3H, $3CH^{Ar}$), 3.78 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): d = 152.9 (C=*C*-S), 147.9 ($C^{Ar\text{-}q}$), 132.8 (CH^{Ar}), 131.1 ($C^{Ar\text{-}q}$), 130.8 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 129.6 (CH^{Ar}), 128.7 ($C^{Ar\text{-}q}$), 128.6 (CH^{Ar}), 125.5 (*C*=C-S), 125.4 (CH^{Ar}), 122.6 (CH^{Ar}), 119.7 (q, J_{CF} = 331.0 Hz, $2CF_3$), 87.9 (CTf_2), 34.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –69.90 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1535 (C=C), 1384, 1106 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{11}F_6NNaO_6S_3$ [*M* + Na]$^+$: 569.9545; found: 569.9512.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8h. From 31 mg (0.209 mmol) of alkyne **7h**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8h** (83 mg, 90%) as a colorless solid; mp 55–57 °C; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.28 (m, 2H, $2CH^{Ar}$), 7.01 (m, 3H, $3CH^{Ar}$), 3.19 (s, 2H, CH_2), 2.02 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 159.0 (C=*C*-S), 131.7 (CH^{Ar}), 130.6 ($C^{Ar\text{-}q}$), 128.9 ($2CH^{Ar}$), 128.0 ($2CH^{Ar}$), 124.0 (*C*=C-S), 120.4 (q, J_{CF} = 331.2 Hz, $2CF_3$), 89.1 (CTf_2), 34.8 (CH_2), 16.8 (SCH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.53 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1606 (C=C), 1382, 1106 (O=S=O), 1205 1606 (C=C), 1382, 1106 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{14}F_6NO_4S_3$ [*M* + NH_4]$^+$: 457.9984; found: 458.0000.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8i. From 10 mg (0.05 mmol) of alkyne **7i**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (97:3) as eluent gave compound **8i** (20 mg, 70%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.56 (m, 2H, $2CH^{Ar}$), 7.36 (m, 3H, $3CH^{Ar}$), 3.30 (s, 2H, CH_2-*cyclobutenyl*), 2.02 (t, 2H, *J* = 7.5 Hz, CH_2), 1.34 (m, 2H, CH_2), 1.22 (m, 2H, CH_2), 0.83 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.9 (C=*C*-S), 132.3 ($2CH^{Ar}$), 130.3 (*C*=C-S), 129.4 ($2CH^{Ar}$), 128.7 (CH^{Ar}), 124.8 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 330.9 Hz, $2CF_3$), 88.0 (CTf_2), 36.7 (CH_2-*cyclobutenyl*), 29.1 (CH_2), 27.5 (CH_2), 22.3 (CH_2), 13.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.33 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1382, 1107 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{20}F_6NO_4S_3$ [*M* + NH_4]$^+$: 500.0453; found: 500.0438.

Bis(trifluoromethylsulfonyl)thiocyclobutene 8j. From 15 mg (0.11 mmol) of alkyne **7j**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8j** (33 mg, 71%) as a colorless oil; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.20 (m, 2H, $2CH^{Ar}$), 6.88 (m, 3H, $3CH^{Ar}$), 5.15 (t, 1H, *J* = 1.3 Hz, C=CH), 2.64 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 138.7 (C=*C*H), 134.9 (*C*=CH), 134.4 ($2CH^{Ar}$), 129.9 ($2CH^{Ar}$), 129.8 (CH^{Ar}), 120.2 (q, J_{CF} = 330.9 Hz, $2CF_3$), 88.2 (CTf_2), 35.3 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.44 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1386, 1106 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{12}F_6NO_4S_3$ [*M* + NH_4]$^+$: 443.9827; found: 443.9839.

Bis(trifluoromethylsulfonyl)selenocyclobutene 8k. From 40 mg (0.17 mmol) of alkyne **7k**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (97:3) as eluent gave compound **8k** (67 mg, 75%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.68 (m, 2H, $2CH^{Ar}$), 7.34 (m, 3H, $3CH^{Ar}$), 3.41 (s, 2H, CH_2-*cyclobutenyl*), 2.03 (t, 2H, *J* = 7.4 Hz, CH_2), 1.26 (m, 4H, $2CH_2$), 0.83 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.4 (*C*=C-Se), 134.2 ($2CH^{Ar}$), 129.5 ($2CH^{Ar}$), 128.7

(CH^{Ar}), 126.9 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.0 Hz, $2CF_3$), 118.7 (C=*C*-Se), 87.8 (CTf_2), 38.3 (CH_2-*cyclobutenyl*), 29.6 (CH_2), 27.4 (CH_2), 22.3 (CH_2), 13.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.35 (s, 6F, $2CF_3$); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 362.22 (s, 1Se, SePh); IR (CH_2Cl_2): ν = 1380, 1106 (O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{20}F_6NO_4S_2Se$ [*M* + NH_4]$^+$: 547.9897; found: 547.9921.

Bis(trifluoromethylsulfonyl)selenocyclobutene 8l. From 32 mg (0.118 mmol) of alkyne **7l**, and after flash chromatography of the residue using neutral alumina hexanes/ethyl acetate (97:3) as eluent gave compound **8l** (29 mg, 43%) as a colorless oil; ^1H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.42 (m, 2H, $2CH^{Ar}$), 7.17 (m, 2H, $2CH^{Ar}$), 6.81 (m, 3H, $3CH^{Ar}$), 6.69 (m, 2H, $2CH^{Ar}$), 3.41 (s, 2H, CH_2), 1.90 (s, 3H, CH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 162.4 (*C*=C-Se), 142.9 ($C^{Ar\text{-}q}$), 131.5 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 129.4 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 127.8 (CH^{Ar}), 127.7 ($C^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 331.5 Hz, $2CF_3$), 112.6 (C=*C*-Se), 89.0 (CTf_2), 36.6 (CH_2), 21.4 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.31 (s, 6F, $2CF_3$); ^{77}Se NMR (95 MHz, C_6D_6, 25 °C): δ = 366.19 (s, 1Se, SePh); IR (CH_2Cl_2): ν = 1604 (C=C), 1381, 1106 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_6KO_4S_2Se$ [*M* + K]$^+$: 602.9034; found: 602.9061.

Bis(trifluoromethylsulfonyl)selenocyclobutene 8m. From 30 mg (0.12 mmol) of alkyne **7m**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (95:5) as eluent gave compound **8m** (64 mg, quantitative yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (m, 2H, $2CH^{Ar}$), 7.51 (m, 3H, $3CH^{Ar}$), 3.76 (s, 2H, CH_2-*cyclobutenyl*), 3.04 (t, 2H, *J* = 7.5 Hz, CH_2), 1.73 (m, 2H, CH_2), 1.33 (m, 4H, $2CH_2$), 0.86 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.6 (*C*=C-Se), 131.9 (CH^{Ar}), 130.7 ($C^{Ar\text{-}q}$), 128.9 ($2CH^{Ar}$), 127.4 ($2CH^{Ar}$), 119.8 (q, J_{CF} = 331.3 Hz, $2CF_3$), 115.0 (C=*C*-Se), 87.8 (CTf_2), 36.4 (CH_2-*cyclobutenyl*), 31.7 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 22.0 (CH_2), 13.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.23 (s, 6F, $2CF_3$); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 245.0 (s, 1Se, Se); IR ($CHCl_3$): ν = 1381, 1106 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{22}F_6NO_4S_2Se$ [*M* + NH_4]$^+$: 562.0054; found: 562.0037.

Bis(trifluoromethylsulfonyl)telurocyclobutene 8n. From 20 mg (0.07 mmol) of alkyne **7n**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (97:3) as eluent gave compound **8n** (30 mg, 73%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.83 (m, 2H, $2CH^{Ar}$), 7.24 (m, 3H, $3CH^{Ar}$), 3.51 (s, 2H, CH_2-*cyclobutenyl*), 1.97 (t, 2H, *J* = 7.4 Hz, CH_2), 1.15 (m, 4H, $2CH_2$), 0.73 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 176.2 (*C*=C-Te), 139.5 ($2CH^{Ar}$), 129.6 ($2CH^{Ar}$), 129.0 (CH^{Ar}), 119.9 (q, J_{CF} = 331.3 Hz, $2CF_3$), 111.9 ($C^{Ar\text{-}q}$), 101.0 (C=*C*-Te), 87.0 (CTf_2), 40.2 (CH_2-*cyclobutenyl*), 31.3 (CH_2), 27.5 (CH_2), 22.3 (CH_2), 13.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.18 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1379, 1106 (O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{20}F_6NO_4S_2Te$ [*M* + NH_4]$^+$: 597.9791; found: 597.9804.

Bis(trifluoromethylsulfonyl)telurocyclobutene 8o. From 20 mg (0.066 mmol) of alkyne **7o**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8o** (31 mg, 80%) as a colorless solid; mp 65–67 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.84 (m, 2H, $2CH^{Ar}$), 7.52 (m, 3H, $3CH^{Ar}$), 3.97 (s, 2H, CH_2-*cyclobutenyl*), 3.03 (t, 2H, *J* = 7.5 Hz, CH_2), 1.81 (m, 2H, CH_2), 1.28 (m, 4H, $2CH_2$), 0.84 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.5 (*C*=C-Te), 132.0 (CH^{Ar}), 131.2 ($C^{Ar\text{-}q}$), 128.8 ($2CH^{Ar}$), 126.8 ($2CH^{Ar}$), 120.0 (q, J_{CF} = 331.6 Hz, $2CF_3$), 92.8 (C=*C*-Te), 86.5 (CTf_2), 38.5 (CH_2-*cyclobutenyl*), 33.8 (CH_2), 30.8 (CH_2), 21.9 (CH_2), 13.8 (CH_3), 11.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.13 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1381, 1107 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{22}F_6O_4S_2Te$ [*M* + NH_4]$^+$: 611.9947; found: 611.9927.

Bis(trifluoromethylsulfonyl)telurocyclobutene 8p. From 50 mg (0.178 mmol) of alkyne **7p**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **8p** (102 mg, quantitative yield) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 3.62 (s, 2H, CH_2-*cyclobutenyl*), 2.90 (t, 2H, *J* = 7.6 Hz, CH_2), 2.43 (t, 2H, *J* = 7.4 Hz, CH_2), 1.82 (m, 2H, CH_2), 1.41 (m, 8H, $4CH_2$), 0.91 (m, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 178.6 (*C*=C-Te), 119.9 (q, J_{CF} = 331.1 Hz, $2CF_3$), 98.3 (C=*C*-Te), 86.5 (CTf_2), 39.8 (CH_2-*cyclobutenyl*), 33.9 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 13.9 (CH_3), 13.7 (CH_3), 10.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –70.27 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1605 (C=C), 1380, 1107 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{26}F_6O_4S_2Te$ [*M* + NH_4]$^{+}$: 592.0260; found: 592.0254.

Thiocyclobutenone 9q. From 40 mg (0.16 mmol) of alkyne **7q**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **9q** (13 mg, 29%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.82 (m, 2H, $2CH^{Ar}$), 7.43 (m, 2H, $2CH^{Ar}$), 7.28 (m, 3H, $3CH^{Ar}$), 7.02 (m, 2H, $2CH^{Ar}$), 3.90 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 185.7 (C=O), 167.2 (C=*C*-SPh), 162.7 ($C^{Ar\text{-}q}$-OCH_3), 132.0 ($2CH^{Ar}$), 131.9 (*C*=C-SPh), 129.9 ($2CH^{Ar}$), 129.0 ($2CH^{Ar}$), 127.1 (CH^{Ar}), 127.0 ($C^{Ar\text{-}q}$), 124.6 ($C^{Ar\text{-}q}$), 114.4 ($2CH^{Ar}$), 55.5 (OCH_3), 49.3 (CH_2); IR ($CHCl_3$): ν = 1757 (C=O), 1601 (C=C), 1260 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}O_2S$ [*M* + H]$^{+}$: 283.0787; found: 283.0790.

Thiocyclobutenone 9r. From 46 mg (0.21 mmol) of alkyne **7r**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **9r** (13 mg, 24%) as a yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.49 (m, 2H, $2CH^{Ar}$), 6.95 (m, 4H, $4CH^{Ar}$), 6.80 (dd, 1H, *J* = 3.7, 1.1 Hz, CH^{Ar}), 6.57 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 3.06 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 183.3 (C=O), 159.6 (C=*C*-SPh), 134.9 ($C^{Ar\text{-}q}$), 133.6 (CH^{Ar}), 132.3 (CH^{Ar}), 132.1 (*C*=C-SPh), 130.7 ($2CH^{Ar}$), 129.3 ($2CH^{Ar}$), 128.0 (CH^{Ar}), 127.4 (CH^{Ar}), 50.4 (CH_2); IR ($CHCl_3$): ν = 1732 (C=O), 1572 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}OS_2$ [*M* + H]$^{+}$: 259.0246; found: 259.0252.

Thiocyclobutenone 9s. From 30 mg (0.12 mmol) of alkyne **7s**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **9s** (15 mg, 42%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.37 (m, 10H, $10CH^{Ar}$), 3.31 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 182.0 (C=O), 172.9 (*C*=C), 134.1 ($2CH^{Ar}$), 131.6 ($C^{Ar\text{-}q}$), 130.4 ($2CH^{Ar}$), 130.1 (CH^{Ar}), 129.6 ($C^{Ar\text{-}q}$), 129.4 ($2CH^{Ar}$), 129.0 ($2CH^{Ar}$), 128.4 (C=*C*), 127.2 (CH^{Ar}), 52.3 (CH_2); IR ($CHCl_3$): ν = 1742 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{13}OS_2$ [*M* + H]$^{+}$: 285.0402; found: 285.0410.

Selenocyclobutenone 9t. From 50 mg (0.17 mmol) of alkyne **7t**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **9t** (14 mg, 25%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.69 (m, 2H, $2CH^{Ar}$), 7.63 (m, 2H, $2CH^{Ar}$), 7.43 (m, 3H, $3CH^{Ar}$), 6.96 (m, 2H, $2CH^{Ar}$), 3.85 (s, 3H, OCH_3), 3.24 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 183.5 (C=O), 160.5 (*C*=C-SePh), 159.5 ($C^{Ar\text{-}q}$-OCH_3), 144.4 ($C^{Ar\text{-}q}$), 135.5 ($2CH^{Ar}$), 129.7 (CH^{Ar}), 129.6 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 126.4 (C=*C*-SePh), 122.9 ($C^{Ar\text{-}q}$), 114.1 ($2CH^{Ar}$), 55.3 (OCH_3), 53.1 (CH_2); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 ^{o}C): δ = 445.94 (s, Se, SePh); IR ($CHCl_3$): ν = 1736 (C=O), 1575 (C=C), 1258 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}O_2Se$ [*M* + H]$^{+}$: 331.0233; found: 331.0239.

Telurocyclobutenone 9u. From 45 mg (0.13 mmol) of alkyne **7u**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **9u** (5 mg, 11%) as a pale yellow oil; ^{1}H NMR (700 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.91 (d, 2H, *J* = 6.9 Hz, $2CH^{Ar}$), 7.52 (m, 2H, $2CH^{Ar}$), 7.47 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.35 (t, 2H, *J* = 7.6 Hz, $2CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 3.84 (s, 3H, OCH_3), 3.25 (s, 2H, CH_2); ^{13}C NMR (175 MHz,

$CDCl_3$, 25 °C): δ = 185.0 (C=O), 159.7 ($C^{Ar\text{-}q}$-OCH_3), 152.7 (*C*=C-TePh), 147.1 ($C^{Ar\text{-}q}$), 140.2 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 129.6 (CH^{Ar}), 127.9 ($2CH^{Ar}$), 123.2 ($C^{Ar\text{-}q}$), 114.2 ($2CH^{Ar}$), 112.2 (C=*C*-TePh), 55.4 (CH_2), 55.3 (OCH_3); IR ($CHCl_3$): ν = 1729 (C=O), 1501 (C=C), 1254 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}O_2Te$ [*M* + H]$^+$: 381.0130; found: 381.0116.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11c. From 30 mg (0.12 mmol) of alkyne **10c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **1c** (30 mg, 46%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.34 (m, 2H, $2CH^{Ar}$), 7.15 (m, 2H, $2CH^{Ar}$), 6.85 (m, 2H, $2CH^{Ar}$), 6.77 (m, 1H, CH^{Ar}), 6.68 (m, 2H, $2CH^{Ar}$), 3.30 (m, 2H, CH_2), 1.90 (m, 3H, CH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 161.7 ($C^{Ar\text{-}q}$), 143.0 (C=*C*-S), 131.2 ($C^{Ar\text{-}q}$), 129.5 ($2CH^{Ar}$), 129.4 ($2CH^{Ar}$), 129.3 ($2CH^{Ar}$), 128.5 ($2CH^{Ar}$), 127.6 (CH^{Ar}), 127.5 ($C^{Ar\text{-}q}$), 120.4 (q, J_{CF} = 331.4 Hz, $2CF_3$), 118.3 (*C*=C-S), 89.6 (CTf_2), 35.0 (CH_2), 21.4 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.36 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1604 (C=C), 1381, 1106 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}F_6NO_4S_3$ [*M* + NH_4]$^+$: 534.0297; found: 534.0283.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11d. From 14 mg (0.054 mmol) of alkyne **10d**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **11d** (15 mg, 51%) as a pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 8.00 (m, 2H, $2CH^{Ar}$), 7.46 (m, 2H, $2CH^{Ar}$), 6.94 (m, 3H, $3CH^{Ar}$), 6.50 (m, 2H, $2CH^{Ar}$), 3.57 (d, 1H, *J* = 15.5 Hz, CH*H-cyclobutenyl*), 3.09 (m, 3H, OCH_3), 2.98 (d, 1H, *J* = 15.5 Hz, C*H*H-*cyclobutenyl*); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 162.6 ($C^{Ar\text{-}q}$-OCH_3), 147.2 (C=*C*-S), 141.2 ($C^{Ar\text{-}q}$), 139.5 (*C*=C-S), 131.8 (CH^{Ar}), 131.3 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 124.2 ($2CH^{Ar}$), 120.6 ($C^{Ar\text{-}q}$), 120.2 (q, J_{CF} = 331.9 Hz, CF_3), 120.1 (q, J_{CF} = 331.7 Hz, CF_3), 114.9 ($2CH^{Ar}$), 85.0 (CTf_2), 54.9 (OCH_3), 33.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.84 (s, 3F, CF_3), –71.37 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1605 (C=C), 1387, 1103 (O=S=O), 1214 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{15}F_6O_6S_3$ [*M* + H]$^+$: 548.9930; found: 548.9952.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11e. From 30 mg (0.117 mmol) of alkyne **10e**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **11e** (20 mg, 31%) as a pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 8.23 (d, 1H, *J* = 7.9, 1.3 Hz, CH^{Ar}), 7.55 (m, 2H, $2CH^{Ar}$), 6.94 (m, 4H, $4CH^{Ar}$), 6.65 (td, 1H, *J* = 7.9, 0.9 Hz, CH^{Ar}), 6.24 (d, 1H, *J* = 8.2 Hz, CH^{Ar}), 3.80 (d, 1H, *J* = 16.0 Hz, CH*H-cyclobutenyl*), 3.13 (d, 1H, *J* = 15.8 Hz, C*H*H-*cyclobutenyl*), 3.12 (m, 3H, OCH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 157.4 ($C^{Ar\text{-}q}$-OCH_3), 153.7 (C=*C*-S), 142.7 ($C^{Ar\text{-}q}$), 134.6 (*C*=C-S), 133.3 (CH^{Ar}), 131.2 (CH^{Ar}), 131.1 (CH^{Ar}), 129.5 ($2CH^{Ar}$), 124.5 ($2CH^{Ar}$), 121.3 (CH^{Ar}), 120.3 (q, J_{CF} = 332.0 Hz, CF_3), 120.1 (q, J_{CF} = 331.9 Hz, CF_3), 117.3 ($C^{Ar\text{-}q}$), 111.0 (CH^{Ar}), 84.9 (CTf_2), 54.6 (OCH_3), 33.3 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.81 (s, 3F, CF_3), –71.23 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1607 (C=C), 1387, 1104 (O=S=O), 1214 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{15}F_6O_6S_3$ [*M* + H]$^+$: 548.9929; found: 548.9911.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11f. From 15 mg (0.064 mmol) of alkyne **10f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound **11f** (18 mg, 53%) as a pale yellow oil; ^{1}H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.92 (d, 1H, *J* = 3.1 Hz, CH^{Ar}), 7.53 (m, 2H, $2CH^{Ar}$), 6.95 (m, 3H, $3CH^{Ar}$), 6.67 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 6.38 (t, 1H, *J* = 4.4 Hz, CH^{Ar}), 3.53 (d, 1H, *J* = 15.7 Hz, CH*H-cyclobutenyl*), 2.93 (d, 1H, *J* = 15.7 Hz, C*H*H-*cyclobutenyl*); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ = 146.0 (C=*C*-S), 141.0 ($C^{Ar\text{-}q}$), 134.1 (CH^{Ar}), 132.3 (*C*=C-S), 132.2 (CH^{Ar}), 131.9 (CH^{Ar}), 129.7 ($2CH^{Ar}$), 128.7 (CH^{Ar}), 127.6 ($C^{Ar\text{-}q}$), 124.1 ($2CH^{Ar}$), 120.2 (q, J_{CF} = 331.8 Hz, CF_3), 119.9 (q, J_{CF} = 331.6 Hz, CF_3), 84.4 (CTf_2), 33.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.74 (s, 3F, CF_3), –71.63 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1386, 1105 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{11}F_6O_5S_4$ [*M* + H]$^+$: 524.9388; found: 524.9400.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11g. From 20 mg (0.12 mmol) of alkyne **10g**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **11g** (26 mg, 47%) as a pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.66 (m, 2H, 2CH^{Ar}), 6.90 (m, 3H, 3CH^{Ar}), 3.53 (d, 1H, *J* = 15.9 Hz, CH*H*-*cyclobutenyl*), 3.22 (d, 1H, *J* = 15.9 Hz, C*H*H-*cyclobutenyl*), 1.90 (s, 3H, $SOCH_3$); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 154.2 (C=*C*-S), 138.6 (*C*=C-S), 131.4 (CH^{Ar}), 129.2 (2CH^{Ar}), 129.1 (2CH^{Ar}), 120.2 (q, J_{CF} = 331.5 Hz, CF_3), 120.1 (q, J_{CF} = 331.7 Hz, CF_3), 84.7 (CTf_2), 37.7 ($SOCH_3$), 33.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.56 (s, 3F, CF_3), –70.77 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1386, 1104 (O=S=O), 1211 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{11}F_6O_5S_3$ [*M* + H]$^+$: 456.9667; found: 456.9658.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 11h. From 20 mg (0.10 mmol) of alkyne **10h**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **11h** (28 mg, 57%) as a pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.69 (m, 2H, 2CH^{Ar}), 6.49 (m, 2H, 2CH^{Ar}), 3.55 (d, 1H, *J* = 15.7 Hz, CH*H*-*cyclobutenyl*), 3.24 (d, 1H, *J* = 15.7 Hz, C*H*H-*cyclobutenyl*), 3.09 (m, 3H, OCH_3), 1.96 (s, 3H, $SOCH_3$); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 162.3 (*C*$^{Ar\text{-}q}$-OCH_3), 149.5 (C=*C*-S), 138.3 (*C*=C-S), 131.3 (2CH^{Ar}), 120.6 (C$^{Ar\text{-}q}$), 120.3 (q, J_{CF} = 331.6 Hz, CF_3), 120.2 (q, J_{CF} = 331.8 Hz, CF_3), 114.8 (2CH^{Ar}), 84.7 (CTf_2), 54.9 (OCH_3), 37.6 ($SOCH_3$), 33.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.75 (s, 3F, CF_3), –70.86 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1606 (C=C), 1386, 1104 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{13}F_6O_6S_3$ [*M* + H]$^+$: 486.9773; found: 486.9783.

Bis(trifluoromethylsulfonyl)sulfonylcyclobutene 11i. From 44 mg (0.16 mmol) of alkyne **10i**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **11i** (90 mg, quantitative yield) as a colorless solid; mp 103–105 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.07 (m, 2H, 2CH^{Ar}), 7.93 (m, 2H, 2CH^{Ar}), 7.71 (m, 1H, CH^{Ar}), 7.59 (m, 2H, 2CH^{Ar}), 6.97 (m, 2H, 2CH^{Ar}), 3.88 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 163.0 (*C*$^{Ar\text{-}q}$-OCH_3), 141.9 (*C*=C-SO_2Ph), 139.1 (C=*C*-SO_2Ph), 137.5 (C$^{Ar\text{-}q}$), 135.0 (CH^{Ar}), 132.5 (2CH^{Ar}), 129.7 (2CH^{Ar}), 127.9 (2CH^{Ar}), 119.6 (q, J_{CF} = 331.5 Hz, $2CF_3$), 119.5 (C$^{Ar\text{-}q}$), 114.3 (2CH^{Ar}), 84.2 (CTf_2), 55.5 (OCH_3), 35.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.51 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1599 (C=C), 1386, 1101 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}F_6NO_7S_3$ [*M* + NH_4]$^+$: 582.0144; found: 582.0155.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13a. From 20 mg (0.07 mmol) of alkyne **12a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **13a** (38 mg, 94%) as a colorless solid; mp 117–119 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.65 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 8.35 (s, 1H, NCH^{Ar}), 7.40 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.15 (m, 1H, CH^{Ar}), 6.98 (m, 1H, CH^{Ar}), 6.84 (m, 1H, CH^{Ar}), 6.65 (m, 4H, 4CH^{Ar}), 3.48 (s, 3H, CH_3), 3.11 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 164.0 (C=O), 152.9 (C=*C*-N), 136.4 (*C*=C-N), 132.5 (CH^{Ar}), 131.7 (CH^{Ar}), 129.1 (2CH^{Ar}), 128.4 (2CH^{Ar}), 128.2 (C$^{Ar\text{-}q}$), 126.9 (C$^{Ar\text{-}q}$), 125.0 (CH^{Ar}), 124.0 (CH^{Ar}), 123.0 (CH^{Ar}), 120.1 (q, J_{CF} = 330.8 Hz, $2CF_3$), 118.9 (C$^{Ar\text{-}q}$), 112.8 (C$^{Ar\text{-}q}$), 112.0 (CH^{Ar}), 90.0 (CTf_2), 51.0 (CH_3), 31.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.44 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1711 (C=O), 1375, 1102 (O=S=O), 1196 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{19}F_6N_2O_6S_2$ [*M* + NH_4]$^+$: 585.0583; found: 585.0559.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13b. From 33 mg (0.14 mmol) of alkyne **12b**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **13b** (27 mg, 33%) as a pale yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.65 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 8.48 (s, 1H, CH^{Ar}), 7.40 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.11 (m, 1H, CH^{Ar}), 6.94 (m, 1H, CH^{Ar}), 6.82 (m, 1H, CH^{Ar}), 6.63 (dd, 1H, *J* = 7.7, 1.7, CH^{Ar}),

6.35 (td, 1H, J = 7.6, 0.9 Hz, CH^{Ar}), 5.99 (d, 1H, J = 8.1 Hz, CH^{Ar}), 3.51 (s, 3H, OCH_3), 3.46 (s, 2H, CH_2), 2.45 ($COOCH_3$); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 164.3 (C=O), 158.9 ($C^{Ar\text{-}q}$-OCH_3), 150.2 (C=*C*-N), 138.1 (*C*=C-N), 134.1 (CH^{Ar}), 132.6 (CH^{Ar}), 130.0 (CH^{Ar}), 126.4 ($C^{Ar\text{-}q}$), 124.6 (CH^{Ar}), 123.5 (CH^{Ar}), 122.5 (CH^{Ar}), 120.7 (CH^{Ar}), 120.2 (q, J_{CF} = 330.9 Hz, $2CF_3$), 118.4 (C^{Arq}), 118.1 ($C^{Ar\text{-}q}$), 111.9 ($C^{Ar\text{-}q}$), 111.8 (CH^{Ar}), 111.3 (CH^{Ar}), 90.8 (CTf_2), 54.6 (OCH_3), 50.9 (OCH_3), 33.2 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.44 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1713 (C=O), 1381, 1105 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{21}F_6N_2O_7S_2$ [M + NH_4]$^+$: 615.0689; found: 615.0693.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13c. From 21 mg (0.10 mmol) of alkyne **12c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **13c** (34 mg, 67%) as a colorless solid; mp 141–143 ºC; ^1H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 8.16 (m, 2H, $2CH^{Ar}$), 7.79 (m, 1H, CH^{Ar}), 7.39 (m, 2H, $2CH^{Ar}$), 7.27 (t, 1H, J = 1.3 Hz, =CH), 3.86 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 164.6 (C=O), 137.5 (HC=*C*-N), 134.3 (H*C*=C-N), 131.6 (CH^{Ar}), 128.2 ($C^{Ar\text{-}q}$), 127.6 ($C^{Ar\text{-}q}$), 126.1 (CH^{Ar}), 125.0 (CH^{Ar}), 122.8 (CH^{Ar}), 120.7 (q, J_{CF} = 330.4 Hz, $2CF_3$), 112.9 (CH^{Ar}), 112.4 ($C^{Ar\text{-}q}$), 89.9 (CTf_2), 51.9 (OCH_3), 34.7 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –71.51 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1713 (C=O), 1386, 1105 (O=S=O), 1198 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{15}F_6N_2O_6S_2$ [M + NH_4]$^+$: 509.0270; found: 509.0272.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13d. From XX mg (0.YY mmol) of alkyne **12d**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **13d** (16 mg, 29%) as a pale yellow oil; ^1H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.68 (d, 1H, J = 8.0 Hz, CH^{Ar}), 8.28 (s, 1H, CH^{Ar}), 7.46 (d, 1H, J = 8.3 Hz, CH^{Ar}), 7.21 (m, 1H, CH^{Ar}), 7.05 (m, 1H, CH^{Ar}), 6.58 (dd, 1H, J = 5.0, 0.9 Hz, CH^{Ar}), 6.47 (dd, 1H, J = 3.7, 0.9 Hz, CH^{Ar}), 6.31 (dd, 1H, J = 4.9, 3.9 Hz, CH^{Ar}), 3.47 (OCH_3), 2.09 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 164.1 (C=O), 146.8 (C=*C*-N), 136.4 (*C*=C-N), 133.7 (CH^{Ar}), 132.1 (CH^{Ar}), 131.9 (CH^{Ar}), 130.3 ($C^{Ar\text{-}q}$), 127.9 (CH^{Ar}), 127.0 ($C^{Ar\text{-}q}$), 124.8 (CH^{Ar}), 124.0 (CH^{Ar}), 122.9 (CH^{Ar}), 120.1 (q, J_{CF} = 330.9 Hz, $2CF_3$), 115.3 ($C^{Ar\text{-}q}$), 112.9 ($C^{Ar\text{-}q}$), 112.1 (CH^{Ar}), 91.0 (CTf_2), 50.9 (OCH_3), 31.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.4 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1710 (C=O), 1383, 1105 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{17}F_6N_2O_6S_3$ [M + NH_4]$^+$: 591.0147; found: 591.0156.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13e. From 30 mg (0.10 mmol) of alkyne **12e**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **13e** (56 mg, 95%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.18 (m, 1H, CH^{Ar}), 7.95 (s, 1H, CH^{Ar}), 7.22 (m, 4H, $4CH^{Ar}$), 6.89 (m, 1H, CH^{Ar}), 6.63 (m, 1H, CH^{Ar}), 6.27 (m, 1H, CH^{Ar}), 3.86 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2), 3.26 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 164.5 (C=O), 159.7 ($C^{Ar\text{-}q}$-OCH_3), 152.6 (C=*C*-N), 135.9 (*C*=C-N), 131.9 (CH^{Ar}), 130.2 (CH^{Ar}), 129.1 ($C^{Ar\text{-}q}$), 126.0 ($C^{Ar\text{-}q}$), 124.6 (CH^{Ar}), 123.6 (CH^{Ar}), 122.1 (CH^{Ar}), 120.6 (CH^{Ar}), 119.7 (CH^{Ar}), 119.6 (q, J_{CF} = 330.6 Hz, $2CF_3$), 118.5 ($C^{Ar\text{-}q}$), 112.3 (CH^{Ar}), 112.0 (CH^{Ar}), 111.8 ($C^{Ar\text{-}q}$), 89.5 (CTf_2), 54.8 (OCH_3), 51.4 (OCH_3), 31.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.12 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1713 (C=O), 1381, 1105 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{21}F_6N_2O_7S_2$ [M + NH_4]$^+$: 615.0689; found: 615.0702.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13f. From 30 mg (0.09 mmol) of alkyne **12f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound **13f** (47 mg, 82%) as a colorless solid; mp 91–93 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.19 (m, 2H, $2CH^{Ar}$), 7.95 (t, 1H, J = 1.9 Hz, CH^{Ar}), 7.93 (s, 1H, CH^{Ar}), 7.35 (t, 1H, J = 8.0 Hz, CH^{Ar}), 7.27 (m, 1H, CH^{Ar}), 7.15 (m, 1H, CH^{Ar}), 7.06 (m, 1H, CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 164.4

(C=O), 149.0 (C=*C*-N), 148.5 ($C^{Ar\text{-}q}$), 135.6 (*C*=C-N), 133.8 (CH^{Ar}), 131.4 (CH^{Ar}), 130.7 (CH^{Ar}), 129.6 ($C^{Ar\text{-}q}$), 126.8 (CH^{Ar}), 126.3 ($C^{Ar\text{-}q}$), 125.1 (CH^{Ar}), 124.1 (CH^{Ar}), 122.9 (CH^{Ar}), 122.7 (CH^{Ar}), 122.0 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 330.7 Hz, $2CF_3$), 112.8 ($C^{Ar\text{-}q}$), 111.6 (CH^{Ar}), 89.3 (CTf_2), 51.7 (OCH_3), 31.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.00 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1714 (C=O), 1541 (O=N=O), 1384, 1106 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{18}F_6N_3O_8S_2$ $[M + NH_4]^+$: 630.0434; found: 630.0456.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13g. From 20 mg (0.08 mmol) of alkyne **12g**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **13g** (36 mg, 84%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.22 (m, 1H, CH^{Ar}), 7.91 (s, 1H, CH^{Ar}), 7.39 (m, 3H, $3CH^{Ar}$), 3.94 (s, 3H, OCH_3), 3.34 (s, 2H, CH_2-*cyclobutenyl*), 2.37 (t, 2H, *J* = 7.5 Hz, CH_2), 1.47 (m, 2H, CH_2), 1.32 (m, 2H, CH_2), 0.84 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.6 (C=O), 161.2 (C=*C*-N), 137.2 (*C*=C-N), 132.2 (CH^{Ar}), 125.8 ($C^{Ar\text{-}q}$), 124.5 (CH^{Ar}), 123.3 (CH^{Ar}), 123.1 ($C^{Ar\text{-}q}$), 121.9 (CH^{Ar}), 119.5 (q, J_{CF} = 330.4 Hz, $2CF_3$), 111.3 ($C^{Ar\text{-}q}$), 110.7 (CH^{Ar}), 89.0 (CTf_2), 51.4 (OCH_3), 32.9 (CH_2-*cyclobutenyl*), 28.8 (CH_2), 27.4 (CH_2), 22.2 (CH_2), 13.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.29 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1714 (C=O), 1383, 1107 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{20}F_6NO_6S_2$ $[M + H]^+$: 548.0631; found: 548.0630.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13h. From 19 mg (0.06 mmol) of alkyne **12h**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **13h** (37 mg, quantitative yield) as a colorless solid; mp 127–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.62 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.52 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 7.38 (m, 1H, CH^{Ar}), 7.34 (d, 1H, *J* = 0.6 Hz, CH^{Ar}), 7.23 (m, 6H, $6CH^{Ar}$), 4.27 (m, 1H, OCH*H*), 4.11 (m, 1H, OC*H*H), 3.62 (s, 2H, CH_2-*cyclobutenyl*), 1.08 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 160.6 (C=O), 156.1 (C=*C*-N), 138.7 (*C*=C-N), 132.4 (CH^{Ar}), 130.4 ($C^{Ar\text{-}q}$), 129.2 ($C^{Ar\text{-}q}$), 129.0 ($2CH^{Ar}$), 128.4 ($2CH^{Ar}$), 126.9 ($C^{Ar\text{-}q}$), 126.1 (CH^{Ar}), 122.8 (CH^{Ar}), 122.4 (CH^{Ar}), 119.7 (q, J_{CF} = 331.3 Hz, CF_3), 119.6 (q, J_{CF} = 331.2 Hz, CF_3), 119.3 ($C^{Ar\text{-}q}$), 114.4 (CH^{Ar}), 113.2 (CH^{Ar}), 91.2 (CTf_2), 61.3 (OCH_2), 31.3 (CH_2-*cyclobutenyl*), 13.9 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.25 (s, 3F, CF_3), –70.29 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1723 (C=O), 1381, 1105 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{21}F_6N_2O_6S_2$ $[M + NH_4]^+$: 599.0740; found: 599.0740.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13i. From 33 mg (0.15 mmol) of alkyne **12i**, and after flash chromatography of the residue using hexanes/ethyl acetate (10:0→97:3) as eluent gave compound **13i** (78 mg, quantitative yield) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.34 (d, 1H, *J* = 0.7 Hz, CH^{Ar}), 7.85 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.39 (m, 5H, $5CH^{Ar}$), 7.17 (m, 3H, $3CH^{Ar}$), 3.78 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 145.7 (C=*C*-N), 139.2 (*C*=C-N), 138.3 (CH^{Ar}), 132.1 (CH^{Ar}), 129.0 ($2CH^{Ar}$), 128.6 ($C^{Ar\text{-}q}$), 128.4 ($2CH^{Ar}$), 128.1 (CH^{Ar}), 124.5 ($C^{Ar\text{-}q}$), 122.8 (CH^{Ar}), 121.7 (CH^{Ar}), 119.8 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.1 Hz, $2CF_3$), 111.1 (CH^{Ar}), 88.6 (CTf_2), 31.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.33 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1677 (C=C), 1388, 1104 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{13}F_6N_2O_4S_2$ $[M + H]^+$: 511.0215; found: 5511.0219.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13j. From 30 mg (0.12 mmol) of alkyne **12j**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **13j** (26 mg, 40%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.89 (d, 1H, *J* = 0.8 Hz, CH^{Ar}), 7.25 (d, 1H, *J* = 7.1 Hz, CH^{Ar}), 7.06 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 6.84 (m, 3H, $3CH^{Ar}$), 6.73 (dd, 1H, *J* = 7.7, 1.6 Hz, CH^{Ar}), 6.39 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 6.11 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 3.68 (s, 2H, CH_2), 2.53 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 158.7 ($C^{Ar\text{-}q}$-OCH_3), 142.3 (C=*C*-N), 140.6 (*C*=C-N), 137.5 (CH^{Ar}), 133.2

(CH^{Ar}), 130.2 (CH^{Ar}), 127.6 (CH^{Ar}), 124.5 ($C^{Ar\text{-}q}$), 122.3 (CH^{Ar}), 121.3 (CH^{Ar}), 120.7 (CH^{Ar}), 120.6 ($C^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 331.4 Hz, $2CF_3$), 118.8 ($C^{Ar\text{-}q}$), 111.1 (CH^{Ar}), 111.0 (CH^{Ar}), 90.0 (CTf_2), 54.4 (OCH_3), 34.2 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –0.52 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1670 (C=C), 1385, 1106 (O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}F_6N_2O_5S_2$ [*M* + H]$^+$: 541.0321; found: 541.0319.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13k. From 36 mg (0.09 mmol) of alkyne **12k**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **13k** (46 mg, 72%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (d, 1H, *J* = 1.8 Hz, CH^{Ar}), 7.48 (m, 2H, $2CH^{Ar}$), 7.37 (d, 1H, *J* = 3.5 Hz, CH^{Ar}), 7.29 (m, 1H, CH^{Ar}), 7.03 (d, 1H, *J* = 8.8 Hz, CH^{Ar}), 6.89 (m, 2H, $2CH^{Ar}$), 6.70 (dd, 1H, *J* = 3.4, 0.6 Hz, CH^{Ar}), 3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 148.9 (C=*C*-N), 133.8 (*C*=C-N), 132.5 ($2CH^{Ar}$), 130.3 ($C^{Ar\text{-}q}$), 129.3 ($2CH^{Ar}$), 127.3 ($C^{Ar\text{-}q}$), 127.2 ($C^{Ar\text{-}q}$), 127.0 (CH^{Ar}), 126.5 (CH^{Ar}), 126.5 (CH^{Ar}), 124.1 (CH^{Ar}), 120.2 ($C^{Ar\text{-}q}$), 119.6 (q, J_{CF} = 330.9 Hz, $2CF_3$), 115.3 ($C^{Ar\text{-}q}$), 113.0 (CH^{Ar}), 106.1 (CH^{Ar}), 89.6 (CTf_2), 31.0 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.21 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1382, 1105 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}Br_2F_6N_2O_4S_2$ [*M* + NH_4]$^+$: 682.8739; found: 682.8761.

Bis(trifluoromethylsulfonyl)aminocyclobutene 13l. From 20 mg (0.07 mmol) of alkyne **12l**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **13l** (37 mg, 88%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.99 (m, 2H, $2CH^{Ar}$), 7.61 (m, 2H, $2CH^{Ar}$), 7.28 (m, 5H, CH^{Ar}), 7.15 (m, 2H, $2CH^{Ar}$), 6.98 (m, 2H, $2CH^{Ar}$), 3.68 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.2 (C=*C*-N), 139.1 (*C*=C-N), 132.5 (CH^{Ar}), 129.2 ($2CH^{Ar}$), 128.7 ($2C^{Ar\text{-}q}$), 128.0 ($2CH^{Ar}$), 126.5 ($2CH^{Ar}$), 124.2 ($2C^{Ar\text{-}q}$), 121.7 ($2CH^{Ar}$), 120.6 ($C^{Ar\text{-}q}$), 120.2 ($2CH^{Ar}$), 119.7 (q, J_{CF} = 331.0 Hz, $2CF_3$), 112.0 ($2CH^{Ar}$), 90.8 (CTf_2), 30.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –69.66 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1665 (C=C), 1378, 1104 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{19}F_6N_2O_4S_2$ [*M* + NH_4]$^+$: 577.0685; found: 577.0708.

Bis(trifluoromethylsulfonyl)phosphinylcyclobutene 21a. From 33 mg (0.10 mmol) of alkyne **20a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2→6:4) as eluent gave compound **21a** (55 mg, 89%) as a colorless solid; mp 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.97 (m, 2H, 2CH), 7.76 (m, 4H, $4CH^{Ar}$), 7.55 (m, 6H, $6CH^{Ar}$), 6.82 (m, 2H, 2CH), 3.79 (s, 3H, OCH_3), 3.22 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.2 (*C*$^{Ar\text{-}q}$-OCH_3), 148.5 (d, J_{CP} = 3.0 Hz, *C*=C-P), 140.1 (d, J_{CP} = 86.1 Hz, C=*C*-P), 132.9 (d, J_{CP} = 2.7 Hz, $2CH^{Ar}$), 131.5 ($2CH^{Ar}$), 131.3 (d, J_{CP} = 10.5 Hz, $4CH^{Ar}$), 129.5 (d, J_{CP} = 109.1 Hz, $2C^{Ar\text{-}q}$), 129.1 (d, J_{CP} = 12.7 Hz, $4CH^{Ar}$), 121.3 (*C*$^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.4 Hz, $2CF_3$), 114.0 ($2CH^{Ar}$), 86.4 (d, J_{CP} = 26.4 Hz, CTf_2), 55.3 (OCH_3), 36.4 (d, J_{CP} = 7.5 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.45 (s, 6F, $2CF_3$); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ = 21.07 [s, P, P(=O)Ph_2]; IR ($CHCl_3$): ν = 1603 (C=C), 1385, 1106 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{20}F_6O_6PS_2$ [*M* + H]$^+$: 625.0338; found: 625.0329.

Bis(trifluoromethylsulfonyl)phosphinylcyclobutene 21b. From 53 mg (0.18 mmol) of alkyne **20b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **21b** (99 mg, 94%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (m, 2H, $2CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 4.76 (m, 2H, 2CH), 3.85 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2), 1.37 (d, 6H, *J* = 6.2 Hz, $2CH_3$), 1.27 (d, 6H, *J* = 6.2 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.1 (*C*$^{Ar\text{-}q}$-OCH_3), 145.6 (d, J_{CP} = 9.9 Hz, *C*=C-P), 136.6 (d, J_{CP} = 188.7 Hz, C=*C*-P), 131.1 ($2CH^{Ar}$), 121.5 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.6 Hz, $2CF_3$), 114.0 ($2CH^{Ar}$), 86.3 (d, J_{CP} = 35.8 Hz, CTf_2), 72.5 (d, J_{CP} = 5.6 Hz, 2CH), 55.3 (OCH_3), 36.0 (d, J_{CP} = 7.9 Hz, CH_2), 24.0 (d, J_{CP} = 4.1 Hz, $2CH_3$), 23.7 (d, J_{CP} = 5.0 Hz, $2CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.57 (s, 6F, $2CF_3$); ^{31}P NMR (121 MHz, $CDCl_3$, 25

ºC): δ = 4.48 [s, P, P=O(O^{i}Pr)$_2$]; IR ($CHCl_3$): ν = 1605 (C=C), 1387, 1103 (O=S=O), 1206 (C–F), 988 (P=O) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{23}F_6O_8PS_2Na$ [*M* + Na]$^+$: 611.0368; found: 611.0353.

Bis(trifluoromethylsulfonyl)thiophosphinylcyclobutene 21c. From 30 mg (0.086 mmol) of alkyne **20c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **21c** (8 mg, 15%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.88 (m, 4H, 4CH^{Ar}), 7.55 (m, 2H, 2CH), 7.46 (m, 6H, 6CH^{Ar}), 6.66 (m, 2H, 2CH), 3.75 (s, 3H, OCH_3), 3.30 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 161.6 (*C*$^{Ar\text{-}q}$-OCH_3), 144.9 (d, J_{CP} = 2.1 Hz, *C*=C-P), 141.4 (d, J_{CP} = 69.2 Hz, C=*C*-P), 132.5 (d, J_{CP} = 3.1 Hz, 2CH^{Ar}), 131.5 (d, J_{CP} = 11.5 Hz, 4CH^{Ar}), 131.4 (2CH^{Ar}), 129.2 (d, J_{CP} = 87.6 Hz, 2C$^{Ar\text{-}q}$), 129.0 (d, J_{CP} = 13.1 Hz, 4CH^{Ar}), 120.9 (*C*$^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.5 Hz, $2CF_3$), 113.6 (2CH^{Ar}), 86.6 (d, J_{CP} = 26.8 Hz, CTf_2), 55.3 (OCH_3), 35.5 (d, J_{CP} = 9.8 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.43 (s, 6F, $2CF_3$); ^{31}P NMR (121 MHz, $CDCl_3$, 25 ºC): δ = 32.36 [s, P, P(=S)Ph$_2$]; IR ($CHCl_3$): ν = 1604 (C=C), 1384, 1103 (O=S=O), 1211 (C–F), 695 (P=S) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{20}F_6O_5PS_3$ [*M* + H]$^+$: 641.0109; found: 641.0135.

Bis(trifluoromethylsulfonyl)silacyclobutene 23b. From 50 mg (0.17 mmol) of alkyne **22b**, and after flash chromatography of the residue using hexanes/ethyl acetate (99:1) as eluent gave compound **23b** (80 mg, 81%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.42 (m, 2H, 2CH^{Ar}), 6.89 (m, 2H, 2CH^{Ar}), 3.84 (s, 3H, OCH_3), 3.32 (s, 2H, CH_2), 1.10 (m, 21H, 3CH + 6CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.3 (*C*=C-Si), 160.7 (*C*$^{Ar\text{-}q}$-OCH_3), 149.0 (C=*C*-Si), 129.9 (2CH^{Ar}), 125.1 (C$^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.1 Hz, $2CF_3$), 113.5 (2CH^{Ar}), 90.1 (CTf_2), 55.2 (OCH_3), 36.2 (CH_2), 18.4 (6CH_3), 11.5 (3CH); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.29 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1614 (C=C), 1379, 1106 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{31}F_6NO_5S_2Si$ [*M* + NH_4]$^+$: 598.1546; found: 598.1566.

{4,4-bis[(trifluoromethyl)sulfonyl]but-1-yn-1-yl}benzene 25a. From 37 mg (0.10 mmol) of alkyne **24a**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **25a** (27 mg, 73%) as a colorless solid; mp 143–145 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 7.26 (m, 5H, 5CH^{Ar}), 3.42 (s, 2H, CH_2). The signal of C*H*Tf_2 is not visible in the ^{1}H-RMN spectrum because of its acidity; ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 132.2 (2CH^{Ar}), 129.1 (2CH^{Ar}), 128.2 (CH^{Ar}), 125.7 (C$^{Ar\text{-}q}$), 122.6 (q, J_{CF} = 328.3 Hz, $2CF_3$), 91.5 (*C*≡C), 79.5 (C≡*C*), 63.4 (CTf_2), 19.9 (CH_2). The signal of *C*HTf_2 is visible in the ^{13}C-RMN spectrum as a quaternary carbon rather than as a CH because of the deprotonation; ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –80.37 (s, 6F, $2CF_3$); IR (acetone): ν = 1340, 1042 (O=S=O), 1190 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_7F_6O_4S_2$ [*M* – H]$^+$: 392.9695; found: 392.9686.

1-{4,4-bis[(trifluoromethyl)sulfonyl]but-1-yn-1-yl}-4-bromobenzene 25b. From 64 mg (0.136 mmol) of alkyne **24b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **25b** (55 mg, 85%) as a colorless solid; mp 165–167 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 7.45 (m, 2H, 2CH^{Ar}), 7.23 (m, 2H, 2CH^{Ar}), 3.41 (s, 2H, CH_2). The signal of C*H*Tf_2 is not visible in the ^{1}H-RMN spectrum because of its acidity; ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 133.9 (2CH^{Ar}), 132.3 (2CH^{Ar}), 124.7 (C$^{Ar\text{-}q}$), 122.4 (q, J_{CF} = 328.0 Hz, $2CF_3$), 121.7 (C$^{Ar\text{-}q}$), 92.9 (*C*≡C), 78.3 (C≡*C*), 63.0 (CTf_2), 19.7 (CH_2). The signal of *C*HTf_2 is visible in the ^{13}C-RMN spectrum as a quaternary carbon rather than as a CH because of the deprotonation; ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –80.39 (s, 6F, $2CF_3$); IR (acetone): ν = 1338, 1040 (O=S=O), 1187 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_6BrF_6O_4S_2$ [*M* – H]$^+$: 472.8780; found: 472.8771.

Bis(trifluoromethylsulfonyl)bis(trifluoromethylsulfonyl)clobutene 26. From 20 mg (0.047 mmol) of alkyne **24c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **26** (21 mg, 61%) as a colorless solid; mp 153–155 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 7.60 (m, 2H, 2CH^{Ar}), 6.96 (m, 2H, 2CH^{Ar}), 3.80 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 3.51 (s, 2H, CH_2-*cyclobutenyl*). The signal of C*H*Tf_2 is not visible in the ^{1}H-RMN spectrum because of its acidity; ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 161.3 (*C*$^{Ar\text{-}q}$-OCH_3), 156.4 (*C*=C), 130.5 (C=*C*), 130.2 (2CH^{Ar}), 123.5 (C$^{Ar\text{-}q}$), 122.6 (q, J_{CF} = 327.7 Hz, $2CF_3$), 120.9 (q, J_{CF} = 331.1 Hz, $2CF_3$-*cyclobutenyl*), 114.9 (2CH^{Ar}), 86.9 (CTf_2-*cyclobutenyl*), 61.2 (CTf_2), 55.8 (OCH_3), 37.5 (CH_2-*cyclobutenyl*), 29.6 (CH_2). The signal of *C*HTf_2 is visible in the ^{13}C-RMN spectrum as a quaternary carbon rather than as a CH because of the deprotonation; ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –72.04 (s, 6F, $2CF_3$-*cyclobutenyl*), –80.10 (s, 6F, $2CF_3$); IR (acetone): ν = 1608 (C=C), 1380, 1099 (O=S=O), 1346, 1042 (O=S=O), 1192 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}F_{12}NO_9S_4$ [*M* + NH_4]$^{+}$: 733.9511; found: 733.9513. CCDC 1438231 contains the supplementary crystallographic data for compound **26** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Bis(trifluoromethylsulfonyl)thiocyclobutene 28a. From 10 mg (0.039 mmol) of alkyne **27a**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **28a** (15 mg, 71%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.65 (m, 2H, 2CH^{Ar}), 7.49 (m, 1H, CH^{Ar}), 7.42 (m, 3H, 3CH^{Ar}), 7.29 (m, 1H, CH^{Ar}), 7.18 (dd, 1H, *J* = 8.0, 1.1 Hz, CH^{Ar}), 7.00 (m, 1H, CH^{Ar}), 3.78 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 162.2 (C=*C*-S), 140.0 (*C*$^{Ar\text{-}q}$), 132.8 (CH^{Ar}), 132.1 (CH^{Ar}), 130.4 (*C*$^{Ar\text{-}q}$), 129.7 (CH^{Ar}), 129.2 (2CH^{Ar}), 128.6 (2CH^{Ar}), 125.7 (CH^{Ar}), 121.2 (*C*=C-S), 120.2 (q, J_{CF} = 331.2 Hz, $2CF_3$), 119.2 (CH^{Ar}), 118.9 (C$^{Ar\text{-}q}$), 89.3 (CTf_2), 35.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.03 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 2129, 2099 (N_3), 1297 (N_3), 1384, 1105 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{15}F_6N_4O_4S_3$ [*M* + NH_4]$^{+}$: 561.0154; found: 561.0130.

Bis(trifluoromethylsulfonyl)alkoxycyclobutene 28b. From 30 mg (0.10 mmol) of alkyne **27b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **28b** (35 mg, 60%) as a pale yellow oil; ^{1}H NMR (700 MHz, C_6D_6, 25 ºC): δ = 7.98 (dd, 1H, *J* = 7.6, 1.6 Hz, CH^{Ar}), 7.46 (m, 2H, 2CH^{Ar}), 7.02 (m, 1H, CH^{Ar}), 6.94 (m, 3H, 3CH^{Ar}), 6.81 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 6.38 (d, 1H, *J* = 8.2 Hz, CH^{Ar}), 4.39 (s, 1H, OH), 4.26 (q, 2H, *J* = 7.1 Hz, OCH_2), 3.24 (s, 3H, OCH_3), 2.94 (d, 1H, *J* = 12.3 Hz, C*H*H-*cyclobutenyl*), 2.82 (d, 1H, *J* = 12.3 Hz, CH*H*-*cyclobutenyl*), 0.89 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (175 MHz, C_6D_6, 25 ºC): δ = 156.8 (*C*$^{Ar\text{-}q}$-OMe), 135.8 (C=*C*-O), 132.1 (2CH^{Ar}), 130.6 (CH^{Ar}), 129.3 (CH^{Ar}), 129.1 (*C*=C-O), 128.7 (2CH^{Ar}), 128.3 (CH^{Ar}), 128.2 (*C*$^{Ar\text{-}q}$), 122.2 (*C*$^{Ar\text{-}q}$), 121.2 (CH^{Ar}), 120.3 (q, J_{CF} = 331.4 Hz, CF_3), 120.2 (q, J_{CF} = 330.2 Hz, CF_3), 111.4 (CH^{Ar}), 88.9 (C≡C), 87.3 (C≡C), 86.3 (CTf_2), 70.8 (OCH_2), 70.5 (*C*^{q}-OH), 55.3 (OCH_3), 29.4 (CH_2-*cyclobutenyl*), 14.7 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –71.08 (s, 3F, CF_3), –71.32 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3601 (OH), 2232 (C≡C), 1681 (C=C), 1384, 1106 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{20}F_6O_7S_2Na$ [*M* + Na]$^{+}$: 621.0447; found: 621.0433.

Bis(trifluoromethylsulfonyl)aminocyclobutene 28c. From 31 mg (0.08 mmol) of alkyne **27c**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **28c** (50 mg, 91%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.63 (d, 1H, *J* = 7.7, Hz, CH^{Ar}), 7.52 (dd, 1H, *J* = 8.4, 0.8 Hz, CH^{Ar}), 7.45 (d, 1H, *J* = 0.8, Hz, CH^{Ar}), 7.26 (m, 12H, 12CH^{Ar}), 5.00 (d, 1H, *J* = 15.7 Hz, OC*H*H), 4.94 (d, 1H, *J* = 15.7 Hz, OCH*H*), 3.62 (s, 2H, CH_2-*cyclobutenyl*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.8 (C=O), 156.4 (C=*C*-N), 138.8 (*C*=C-N), 132.4 (CH^{Ar}), 131.9 (2CH^{Ar}), 129.3

($C^{Ar\text{-}q}$), 129.1 ($C^{Ar\text{-}q}$), 129.0 ($2CH^{Ar}$), 128.7 (CH^{Ar}), 128.4 ($2CH^{Ar}$), 128.2 ($2CH^{Ar}$), 126.8 ($C^{Ar\text{-}q}$), 126.5 (CH^{Ar}), 122.9 (CH^{Ar}), 122.6 (CH^{Ar}), 122.2 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.3 Hz, CF_3), 119.6 (q, J_{CF} = 331.5 Hz, CF_3), 118.9 ($C^{Ar\text{-}q}$), 115.4 (CH^{Ar}), 113.3 (CH^{Ar}), 91.3 (CTf_2), 86.6 (*C*≡C), 82.6 (C≡*C*), 53.7 (OCH_2), 31.4 (CH_2-*cyclobutenyl*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.19 (s, 3F, CF_3), –70.26 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1730 (C=O), 1382, 1105 (O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{30}H_{23}F_6N_2O_6S_2$ [*M* + NH_4]$^+$: 685.0896; found: 685.0911.

Bis(trifluoromethylsulfonyl)thiocyclobutene 29a. From 15 mg (0.027 mmol) of azide **28a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **29a** (17 mg, 85%) as a yellow oil; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 8.80 (s, 1H, CH-*triazolyl*), 7.87 (m, 2H, $2CH^{Ar}$), 7.76 (m, 1H, CH^{Ar}), 7.63 (m, 1H, CH^{Ar}), 7.54 (m, 4H, $4CH^{Ar}$), 7.49 (m, 1H, CH^{Ar}), 3.68 (s, 2H, CH_2); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 165.9 (C=*C*-S), 139.5 ($C^{Ar\text{-}q}$-Tf), 136.1 (*C*=C-S), 134.5 (CH^{Ar}), 133.7 (CH^{Ar}), 133.1 (CH^{Ar}), 131.8 (CH^{Ar}), 130.1 (CH^{Ar}), 129.5 ($2CH^{Ar}$), 129.3 ($C^{Ar\text{-}q}$), 128.1 ($2CH^{Ar}$), 127.4 ($C^{Ar\text{-}q}$), 127.1 (CH^{Ar}), 119.6 (q, J_{CF} = 330.8 Hz, $2CF_3$), 119.4 (q, J_{CF} = 324.4 Hz, CF_3), 116.7 ($C^{Ar\text{-}q}$), 88.0 (CTf_2), 35.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.44 (s, 6F, $2CF_3$), –78.50 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1385, 1104 (O=S=O), 1214 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{16}F_9N_4O_6S_4$ [*M* + NH_4]$^+$: 718.9803; found: 718.9797.

Bis(trifluoromethylsulfonyl)aminobis(cyclobutene) 29c. From 50 mg (0.07 mmol) of alkyne **28c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **29c** (44 mg, 62%) as a colorless oil; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.74 (d, 1H, *J* = 7.6, Hz, CH^{Ar}), 7.54 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 7.50 (m, 3H, $3CH^{Ar}$), 7.45 (m, 1H, CH^{Ar}), 7.40 (m, 7H, $7CH^{Ar}$), 7.29 (m, 2H, $2CH^{Ar}$), 5.29 (d, 1H, *J* = 15.5 Hz, OC*H*H), 5.10 (d, 1H, *J* = 15.5 Hz, OCH*H*), 3.77 (d, 1H, *J* = 14.4 Hz, C*H*H-*cyclobutenyl*), 3.71 (d, 1H, *J* = 14.1 Hz, CH*H*-*cyclobutenyl*), 3.26 (s, 2H, CH_2-*cyclobutenyl*); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 159.8 (C=O), 156.0 (C=*C*-N), 148.5 (*C*=C), 138.9 (*C*=C-N), 134.6 (C=*C*), 132.8 (CH^{Ar}), 130.1 (CH^{Ar}), 129.3 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 128.7 ($C^{Ar\text{-}q}$), 128.3 ($2CH^{Ar}$), 128.2 ($C^{Ar\text{-}q}$), 128.0 ($2CH^{Ar}$), 126.9 (CH^{Ar}), 126.7 ($C^{Ar\text{-}q}$), 123.2 (CH^{Ar}), 122.7 (CH^{Ar}), 119.7 (q, J_{CF} = 329.4 Hz, CF_3), 119.6 (q, J_{CF} = 331.9 Hz, CF_3), 119.3 (q, J_{CF} = 330.7 Hz, CF_3), 118.8 ($C^{Ar\text{-}q}$), 116.3 (CH^{Ar}), 113.3 (CH^{Ar}), 91.1 (CTf_2), 85.9 (CTf_2), 59.9 (OCH_2), 35.8 (CH_2-*cyclobutenyl*), 31.4 (CH_2-*cyclobutenyl*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.20 (s, 3F, CF_3), –70.46 (s, 3F, CF_3), –70.51 (s, 3F, CF_3), –70.67 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1724 (C=O), 1381, 1106 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{34}H_{25}F_{12}N_2O_{10}S_4$ [*M* + NH_4]$^+$: 977.0194; found: 977.0215.

General procedure for the uncatalyzed reaction of heteroatom-substituted alkynes 12m–t and pyridinium salt 1d. **Synthesis of cyclobutenones 14m–t**. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.2 mmol) was added at room temperature to a solution of the appropriate ynamine **12m–t** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC). Saturated potassium carbonate (2 mL) was added and the mixture was stirred for 10 minutes, before being partitioned between ethyl acetate and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **14m–t** follow.

Aminocyclobutenone 14m. From 33 mg (0.10 mmol) of alkyne **12m**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **14m** (33 mg, 86%) as a pale yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 8.68 (m, 1H,

CH^{Ar}), 8.02 (s, 1H, CH^{Ar}), 7.26 (m, 2H, $2CH^{Ar}$), 7.11 (m, 1H, CH^{Ar}), 6.97 (m, 2H, $2CH^{Ar}$), 6.44 (m, 2H, $2CH^{Ar}$), 3.60 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 2.96 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 182.2 (C=O), 164.5 (C=O), 162.9 ($C^{Ar\text{-}q}$-OCH_3), 156.7 (C=*C*-N), 135.7 (*C*=C-N), 132.4 ($2CH^{Ar}$), 132.3 (CH^{Ar}), 127.1 ($C^{Ar\text{-}q}$), 124.0 (CH^{Ar}), 123.4 (CH^{Ar}), 123.1 ($C^{Ar\text{-}q}$), 122.6 (CH^{Ar}), 114.5 ($2CH^{Ar}$), 113.2 (CH^{Ar}), 111.2 ($C^{Ar\text{-}q}$), 55.0 (OCH_3), 50.8 (OCH_3), 45.9 (CH_2); IR (CH_2Cl_2): ν = 1762 (C=O), 1706 (C=O), 1600 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{18}NO_4$ [*M* + H]$^+$: 348.1230; found: 348.1240.

Aminocyclobutenone 14n. From 33 mg (0.10 mmol) of alkyne **12n**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **14n** (9 mg, 23%) as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.20 (d, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.98 (s, 1H, CH^{Ar}), 7.35 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.27 (m, 1H, CH^{Ar}), 7.18 (m, 2H, $2CH^{Ar}$), 6.59 (dd, 1H, *J* = 8.6, 2.3 Hz, CH^{Ar}), 6.36 (d, 1H, *J* = 2.3 Hz, CH^{Ar}), 3.93 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2), 3.14 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 184.5 (C=O), 165.2 (C=O), 165.1 ($C^{Ar\text{-}q}$-OCH_3), 160.4 ($C^{Ar\text{-}q}$-OCH_3), 154.7 (C=*C*-N), 136.8 (*C*=C-N), 133.5 (CH^{Ar}), 133.3 (CH^{Ar}), 128.0 ($C^{Ar\text{-}q}$), 125.6 ($C^{Ar\text{-}q}$), 123.4 (CH^{Ar}), 122.5 (CH^{Ar}), 121.5 (CH^{Ar}), 113.6 ($C^{Ar\text{-}q}$), 112.1 (CH^{Ar}), 109.1 ($C^{Ar\text{-}q}$), 105.6 (CH^{Ar}), 98.2 (CH^{Ar}), 55.7 (OCH_3), 54.8 (OCH_3), 51.1 (OCH_3), 47.1 (CH_2); IR ($CHCl_3$): ν = 1760 (C=O), 1707 (C=O), 1605 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_5$ [*M* + H]$^+$: 378.1336; found: 378.1337.

Aminocyclobutenone 14o. From 33 mg (0.10 mmol) of alkyne **12o**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **14o** (15 mg, 42%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (d, 1H, *J* = 1.8 Hz, CH^{Ar}), 7.44 (m, 2H, $2CH^{Ar}$), 7.38 (d, 1H, *J* = 3.4 Hz, CH^{Ar}), 7.29 (m, H, CH^{Ar}), 7.07 (d, 1H, *J* = 8.7 Hz, CH^{Ar}), 6.97 (m, 2H, $2CH^{Ar}$), 6.64 (d, 1H, *J* = 3.3 Hz, CH^{Ar}), 3.88 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 184.0 (C=O), 162.7 ($C^{Ar\text{-}q}$-OCH_3), 155.1 (C=*C*-N), 133.3 (*C*=C-N), 132.2 ($2CH^{Ar}$), 130.3 ($C^{Ar\text{-}q}$), 128.9 ($C^{Ar\text{-}q}$), 127.2 (CH^{Ar}), 125.6 (CH^{Ar}), 123.7 (CH^{Ar}), 123.3 ($C^{Ar\text{-}q}$), 114.5 ($2CH^{Ar}$), 113.9 (CH^{Ar}), 104.8 (CH^{Ar}), 55.6 (OCH_3), 45.7 (CH_2); IR ($CHCl_3$): ν = 1763 (C=O), 1602 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{15}BrNO_2$ [*M* + H]$^+$: 368.0281; found: 368.0292.

Aminocyclobutenone 14p. From 20 mg (0.07 mmol) of alkyne **12p**, and after flash chromatography of the residue using hexanes/ethyl acetate (85:15) as eluent gave compound **14p** (20 mg, 88%) as a colorless solid; mp 154–156 °C; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.96 (d, 2H, *J* = 7.7 Hz, $2CH^{Ar}$), 7.41 (d, 2H, *J* = 8.0 Hz, $2CH^{Ar}$), 7.28 (m, 2H, $2CH^{Ar}$), 7.21 (m, 2H, $2CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 6.38 (m, 2H, $2CH^{Ar}$), 3.11 (s, 2H, CH_2). 3.07 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 183.8 (C=O), 162.5 ($C^{Ar\text{-}q}$-OCH_3), 157.7 (C=*C*-N), 139.0 ($2C^{Ar\text{-}q}$), 132.9 ($2CH^{Ar}$), 128.7 (*C*=C-N), 126.5 ($2CH^{Ar}$), 124.5 ($2C^{Ar\text{-}q}$), 123.9 ($C^{Ar\text{-}q}$), 121.3 ($2CH^{Ar}$), 120.7 ($2CH^{Ar}$), 114.3 ($2CH^{Ar}$), 112.5 ($2CH^{Ar}$), 54.8 (OCH_3), 45.5 (CH_2); IR (CH_2Cl_2): ν = 1760 (C=O), 1602 (C=C), 1262 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{18}NO$ [*M* + H]$^+$: 340.1332; found: 340.1324.

Aminocyclobutenone 14q. From 30 mg (0.10 mmol) of alkyne **12q**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **14q** (19 mg, 53%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.39 (d, 1H, *J* = 0.7 Hz, CH^{Ar}), 7.19 (m, 5H, $5CH^{Ar}$), 7.03 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 6.80 (m, 2H, $2CH^{Ar}$), 4.23 (q, 2H, *J* = 7.1 Hz, CH_2), 3.75 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2-*cyclobutenyl*), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 185.4 (C=O), 162.7 (C=O), 160.9 ($C^{Ar\text{-}q}$-OCH_3), 137.3 (*C*=C-N), 132.2 ($2CH^{Ar}$), 128.8 ($C^{Ar\text{-}q}$), 128.3 ($C^{Ar\text{-}q}$), 126.8 ($C^{Ar\text{-}q}$), 125.9 (CH^{Ar}), 123.3 ($C^{Ar\text{-}q}$), 122.8 (CH^{Ar}), 121.9 (CH^{Ar}), 114.5 ($2CH^{Ar}$), 112.6 (CH^{Ar}), 112.1 (CH^{Ar}), 60.9 (OCH_2), 55.4 (OCH_3), 44.8 (CH_2-*cyclobutenyl*),

14.2 (CH_3); IR ($CHCl_3$): ν = 1769 (C=O), 1715 (C=O), 1602 (C=C), 1207 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_4$ [*M* + H]$^+$: 362.1387; found: 362.1385.

Aminocyclobutenone 14r. From 31 mg (0.10 mmol) of alkyne **12r**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **14r** (15 mg, 45%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.51 (s, 1H, CH^{Ar}), 7.38 (s, 1H, CH^{Ar}), 7.32 (m, 2H, $2CH^{Ar}$), 7.11 (dd, 1H, *J* = 8.6, 1.4 Hz, CH^{Ar}), 6.99 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 6.88 (m, 2H, $2CH^{Ar}$), 4.30 (q, 2H, *J* = 7.1 Hz, CH_2), 3.83 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2-*cyclobutenyl*), 2.45 (s, 3H, CH_3), 1.32 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 185.4 (C=O), 162.7 (C=O), 160.9 ($C^{Ar\text{-}q}$-OCH_3), 160.6 (C=*C*-N), 135.8 (*C*=C-N), 132.2 ($2CH^{Ar}$), 131.4 ($C^{Ar\text{-}q}$), 129.1 ($C^{Ar\text{-}q}$), 128.3 ($C^{Ar\text{-}q}$), 127.8 (CH^{Ar}), 127.1 ($C^{Ar\text{-}q}$), 123.4 ($C^{Ar\text{-}q}$), 122.2 (CH^{Ar}), 114.5 ($2CH^{Ar}$), 112.1 (CH^{Ar}), 111.8 (CH^{Ar}), 60.8 (OCH_2), 55.5 (OCH_3), 44.8 (CH_2-*cyclobutenyl*), 21.3 (CH_3), 14.2 (CH_3); IR ($CHCl_3$): ν = 1769 (C=O), 1714 (C=O), 1602 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{22}NO_4$ [*M* + H]$^+$: 376.1543; found: 376.1538.

Aminocyclobutenone 14s. From 34 mg (0.10 mmol) of alkyne **12s**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **14s** (20 mg, 51%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.72 (d, 1H, *J* = 1.9 Hz, CH^{Ar}), 7.39 (s, 1H, CH^{Ar}), 7.28 (m, 2H, $2CH^{Ar}$), 7.24 (dd, 1H, *J* = 8.9, 2.0 Hz, CH^{Ar}), 7.04 (d, 1H, *J* = 8.9 Hz, CH^{Ar}), 6.89 (m, 2H, $2CH^{Ar}$), 4.31 (q, 2H, *J* = 7.1 Hz, CH_2), 3.84 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2-*cyclobutenyl*), 1.33 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 185.0 (C=O), 163.0 (C=O), 161.3 ($C^{Ar\text{-}q}$-OCH_3), 160.5 (C=*C*-N), 135.6 (*C*=C-N), 132.2 ($2CH^{Ar}$), 129.5 ($C^{Ar\text{-}q}$), 128.2 ($C^{Ar\text{-}q}$), 127.7 ($C^{Ar\text{-}q}$), 127.6 ($C^{Ar\text{-}q}$), 126.3 (CH^{Ar}), 123.1 ($C^{Ar\text{-}q}$), 122.0 (CH^{Ar}), 114.6 ($2CH^{Ar}$), 113.2 (CH^{Ar}), 111.6 (CH^{Ar}), 61.2 (OCH_2), 55.5 (OCH_3), 44.9 (CH_2-*cyclobutenyl*), 14.2 (CH_3); IR ($CHCl_3$): ν = 1770 (C=O), 1717 (C=O), 1627 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{19}ClNO_4$ [*M* + H]$^+$: 396.0997; found: 396.0988.

Aminocyclobutenone 14t. From 18 mg (0.05 mmol) of alkyne **12t**, and after flash chromatography of the residue using hexanes/ethyl acetate (93:7) as eluent gave compound **14t** (8 mg, 41%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.81 (d, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.70 (d, 1H, *J* = 0.8 Hz, CH^{Ar}), 7.35 (m, 6H, $6CH^{Ar}$), 7.19 (m, 4H, $4CH^{Ar}$), 6.90 (m, 2H, $2CH^{Ar}$), 3.84 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 185.3 (C=O), 162.9 (C=O), 161.3 ($C^{Ar\text{-}q}$-OCH_3), 150.4 ($C^{Ar\text{-}q}$), 137.8 (C=*C*-N), 132.3 ($2CH^{Ar}$), 132.2 (*C*=C-N), 129.4 ($2CH^{Ar}$), 128.4 ($C^{Ar\text{-}q}$), 127.2 ($C^{Ar\text{-}q}$), 126.8 ($C^{Ar\text{-}q}$), 126.5 (CH^{Ar}), 125.9 (CH^{Ar}), 123.3 ($C^{Ar\text{-}q}$), 123.1 (CH^{Ar}), 122.2 (CH^{Ar}), 121.7 ($2CH^{Ar}$), 114.5 ($2CH^{Ar}$), 114.0 (CH^{Ar}), 112.2 (CH^{Ar}), 55.5 (OCH_3), 44.9 (CH_2); IR ($CHCl_3$): ν = 1767 (C=O), 1732 (C=O), 1601 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{26}H_{20}NO_4$ [*M* + H]$^+$: 410.1387; found: 410.1400.

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VI. CAPÍTULO 3

VI.1. Direct Metal-Free Entry to Aminocyclobutenes or Aminocyclobutenols from Ynamides: Synthetic Applications

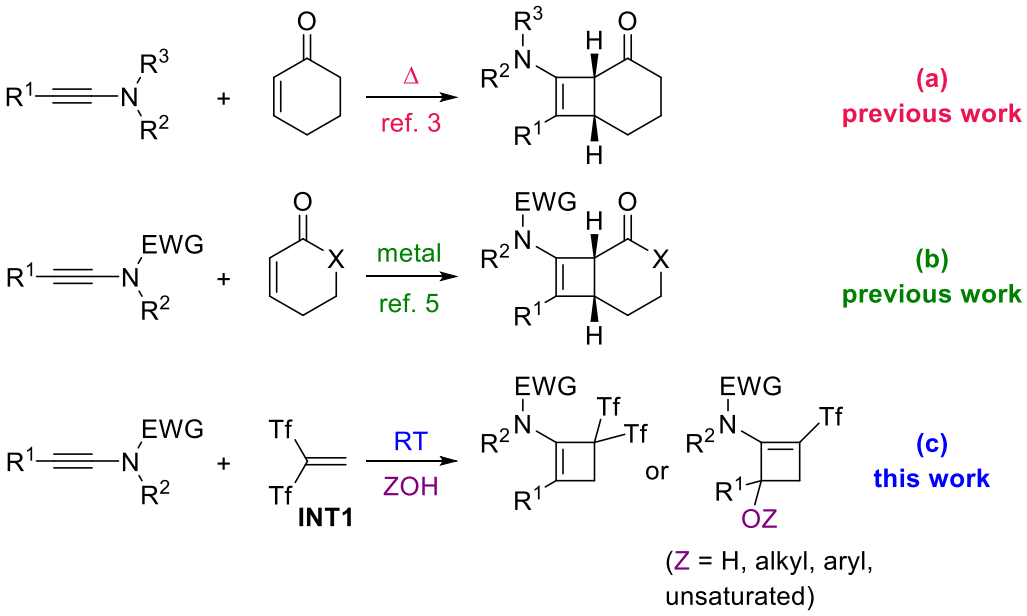
The [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ has been developed to regioselectively afford bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with the ynamides bearing electron-rich aromatic rings at the C-terminal, an interesting reactivity switch was observed; a cyclization/ hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. Aminocyclobutene construction with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3- (triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

Chem. Eur. J. **2016**, *22*, 8998

VI.2. Article

VI.2.1. Introduction

Functionalized cyclobutenes are important scaffolds present in several bioactive compounds, which have also been used as synthetic intermediates for the preparation of functionalized organic molecules.[1] Of particular interest is the aminocyclobutene structural motif.[2] A traditional method for aminocyclobutene preparation in a single step is the Ficini reaction, a [2+2] cycloaddition of ynamines with cyclic electron-deficient alkenes (Scheme VI.1a).[3] However, the Ficini reaction presents a serious drawback, owing to the difficulty of preparing and handling reactive ynamines. More recently, ynamides,[4] which bear increased stability, has been proved as convenient substrates for the Ficini reaction (Scheme VI.1b).[5] Unfortunately, their widespread use in aminocyclobutene synthesis is precluded by the narrow substrate scope of the alkene partner, which is normally a cyclic α,β-unsaturated carbonyl compound. An additional drawback is the use of environmentally unfriendly or expensive metallic salts, which are required for the activation of ynamides. Consequently, efficient metal-free synthesis of functionalized aminocyclobutenes with high chemo- and regioselectivity remains a challenge.



Scheme VI.1. [2+2] cycloadditions of ynamides with alkenes.

We contemplated a possible mild, metal-free synthesis of aminocyclobutenes through the reaction of the highly polarized reagent 1,1-bis(trifluoromethylsulfonyl)ethene **INT1**[6] with ynamides (Scheme VI.1c). Of practical interest, 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** was identified as a stable precursor of **INT1** with the transference of the $Tf_2C{=}CH_2$ group to phenols, alkynes, 1,3-dienes, and azides.[7] Herein we describe the discovery and development of the uncatalyzed [2+2] cycloaddition of ynamides with $Tf_2C{=}CH_2$ **INT1** under mild conditions. Incidentally, with ynamides bearing electron-rich aromatic rings at the C-terminal, we observed an interesting reactivity switch.

VI.2.2. Results and discussion

Figure VI.1 and Figure VI.2 show the structures of starting ynamides **30a–j** and **30k–z'**, respectively.

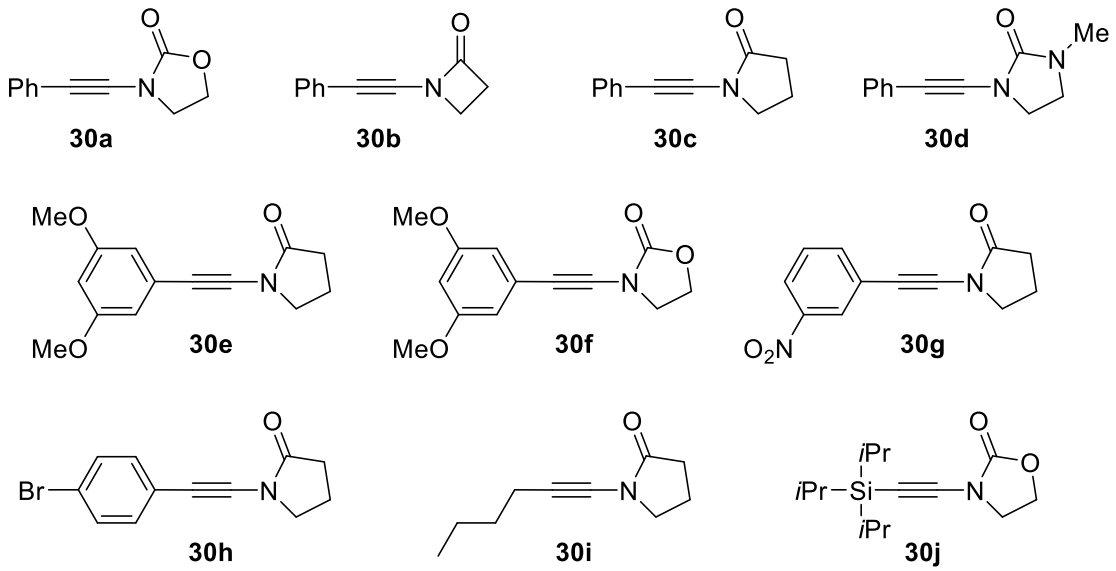


Figure VI.1. Structures of starting ynamides **30a–j**.

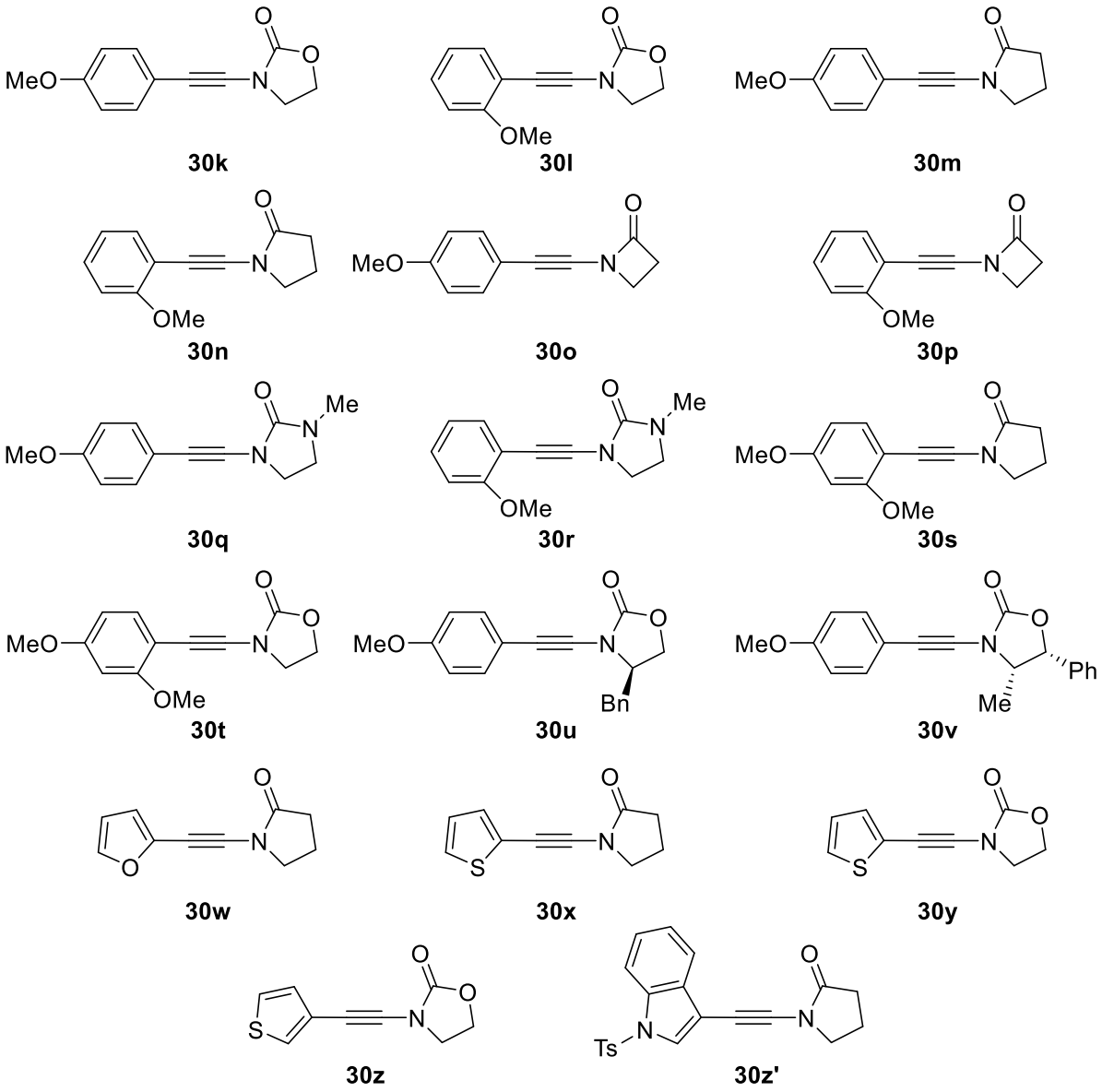
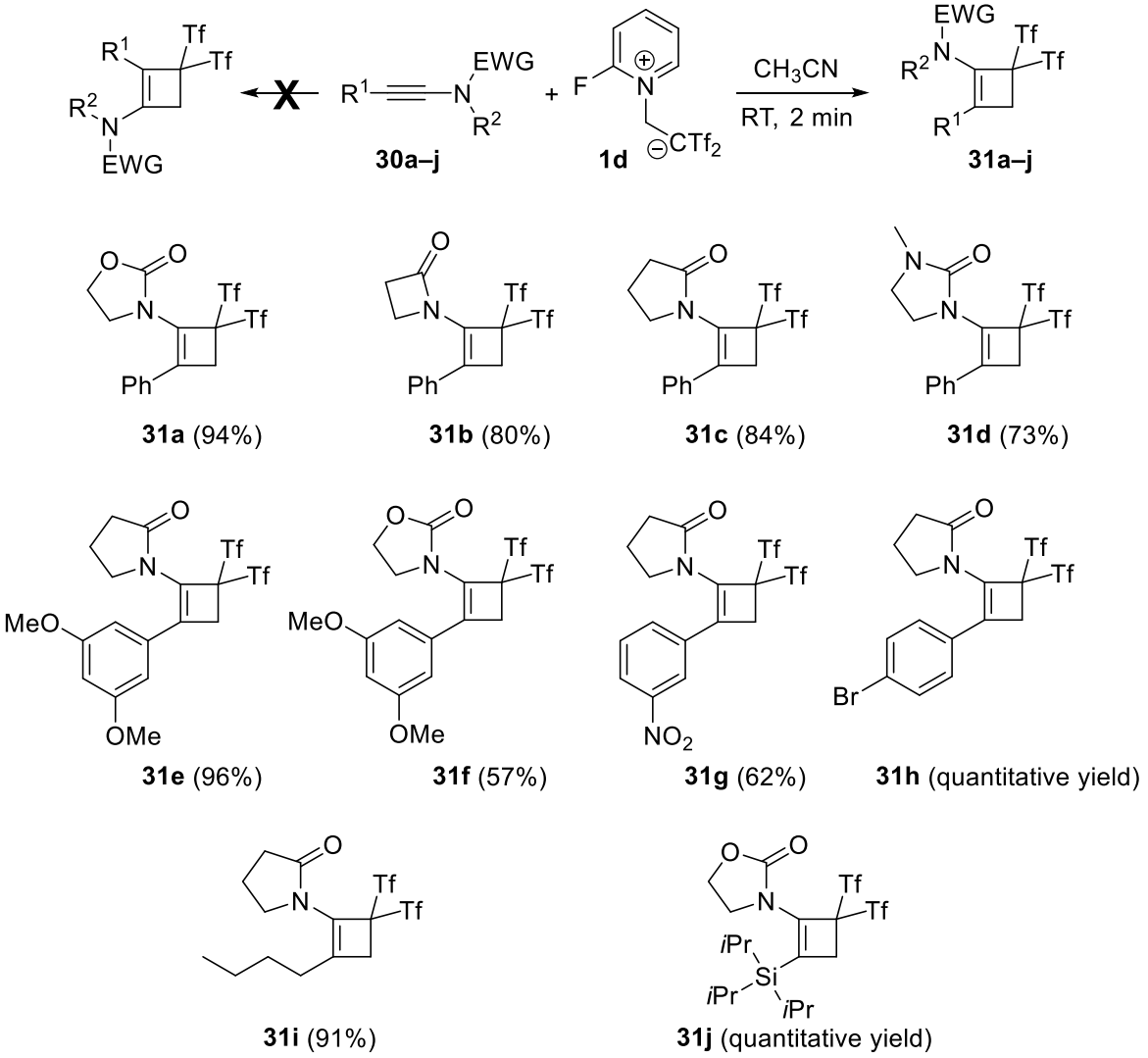


Figure VI.2. Structures of starting ynamides **30k–z'**.

Initially we treated the oxazolidinone-based phenyl ynamide **30a** with zwitterion **1d** in acetonitrile at room temperature (the optimal conditions identified earlier in our laboratory for the reaction of pyridinium salt **1d**).[7c,d] The nitrogenated functionality of ynamides can either become part of a possible five-membered azaheterocycle or be introduced as an amino substituent onto the required cyclobutene. Happily, the desired 4,4-bis(trifluoromethylsulfonyl)-cyclobut-1-enamide **31a** was cleanly formed with total regioselectivity and isolated in an excellent 94% yield (Scheme VI.2). It is important to note that excess of pyridinium salt **1d** was not required and the use of equimolecular amounts of zwitterion was

enough, thus not generating additional waste. Next, we decide to evaluate the generality of the reaction with respect to nitrogen functionalization. Azetidin-2-one-, pyrrolidin-2-one-, and imidazolidin-2-one-based phenyl ynamides **30b–d** were selected as the substrates to test our cyclization reaction.

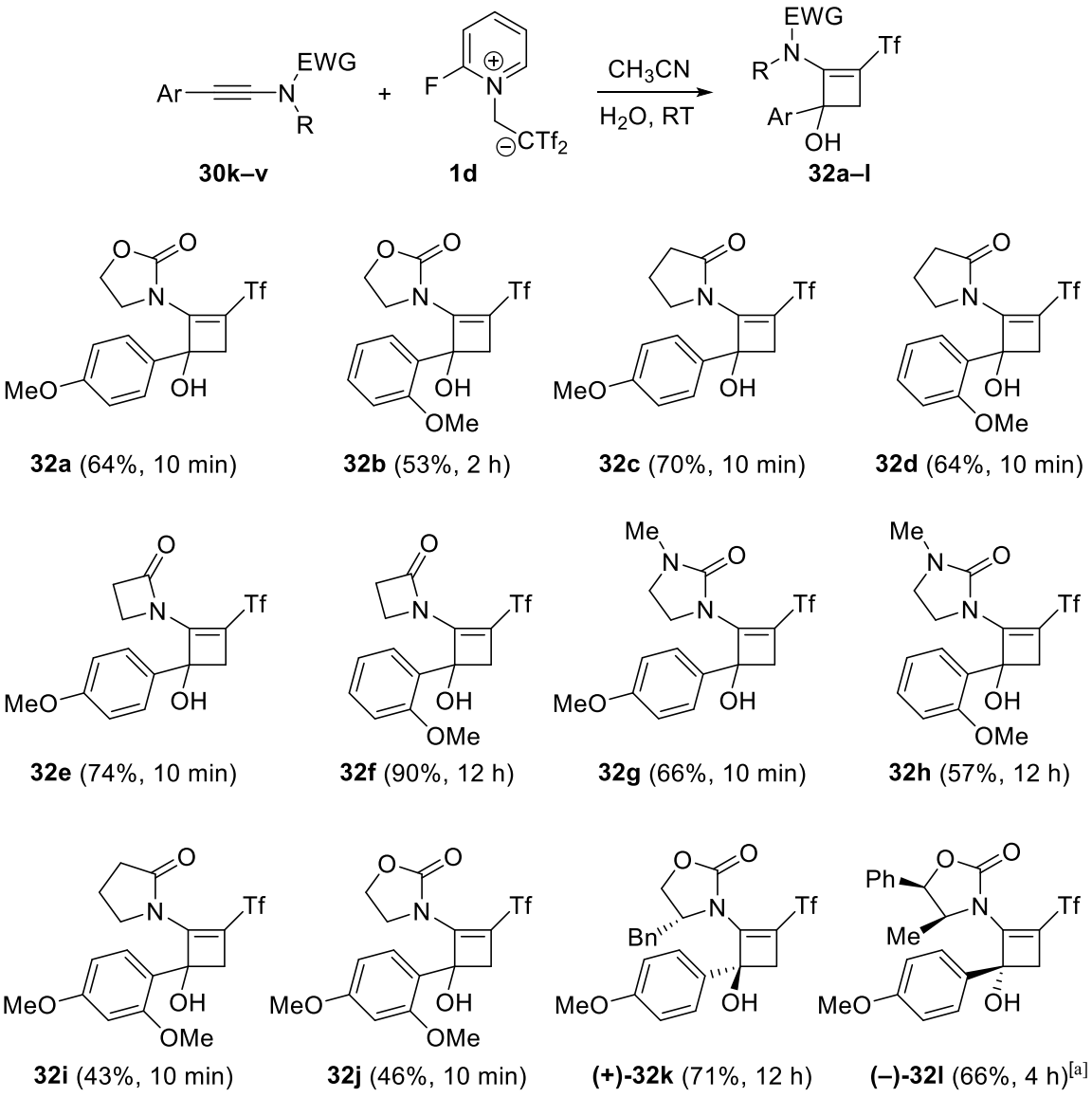


Scheme VI.2. Uncatalyzed reaction of ynamides **30** with zwitterion **1d**. Controlled synthesis of 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **31**.

We were pleased to find that the desired four-membered carbocyclic products **31b–d** were smoothly obtained (Scheme VI.2). We then turned to examine a series of ynamides by varying substitution on the *C*-terminal. Thus, dimethoxyphenyl, nitrophenyl, and bromophenyl ynamides **30e–h** afforded adducts **31e–h** in 57%-quantitative yields (Scheme VI.2). The process was not limited to aromatic ynamides;

alkyl-substituted ynamide **30i** also performed well to produce the expected product **31i**. Likewise, the silyl-protected acetylene **30j** survived the reaction very well to form **4j** in quantitative yield (Scheme VI.2). Ynamides that contained substituents with different electronic features were well-tolerated; with the present method becoming a facile route to aminocyclobutene scaffolds. Notably, ynamides **30a–j** instantaneously reacted to selectively give the corresponding aminocyclobutenes **31a–j**.[8]

Next, the general scope of the reaction with ynamides that contained electron-donating methoxy groups at the *ortho* or *para* positions of the benzene ring was examined. When electron-rich ynamides **30k–v** were subjected to the above conditions used for ynamides **30a–j**, a remarkable effect of the electronic properties of the starting alkyne on the product formation was observed. There was no evidence of the presence of type **31** products, with compounds **31k–v** probably undergoing further reaction. To our delight, acetylene derivatives **30k–y** underwent an appealing cyclization/hydroxylation sequence, yielding novel 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **32a–j** (Scheme VI.3).



Scheme VI.3. Uncatalyzed reaction of ynamides 3 with zwitterion **1d**. Controlled synthesis of 1-aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **32**. [a] Major isomer is shown (d.r.=80:20).

A gram-scale synthesis of **32f** demonstrated the robustness of this methodology. Complete conversion was observed by thin-layer chromatography (TLC) and ^{1}H NMR spectroscopy of the crude reaction mixtures in all cases. However, side reactions were detected on highly activated ynamides **30s** and **30t**, which may be responsible for the moderate yields of isolated adducts **32i** and **32j**. To test the importance of the steric effects, enantiopure chiral ynamides **30u** and **30v** were prepared and tested. Despite the steric hindrance from the oxazolidinone substituents, aminocyclobutenols **32k** and **32l** were obtained in reasonable yields

(Scheme VI.3). Adduct **32k** was obtained as single enantiomer, whereas adduct **32l** was obtained as an 80:20 diastereomeric mixture. For conclusive assessment of the structure of compounds **32**, an X-ray crystallographic analysis of adduct **32a** was undertaken (Figure VI.3).[9]

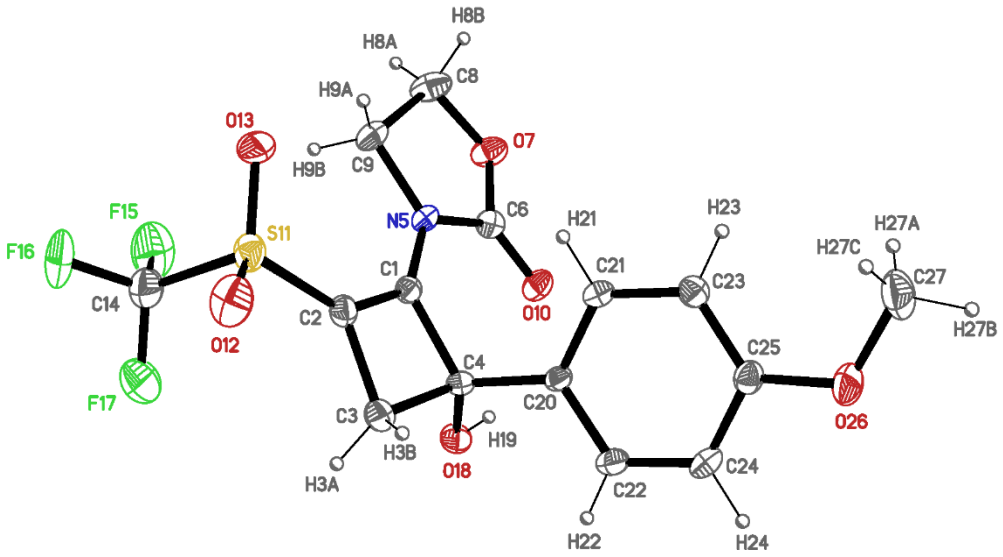
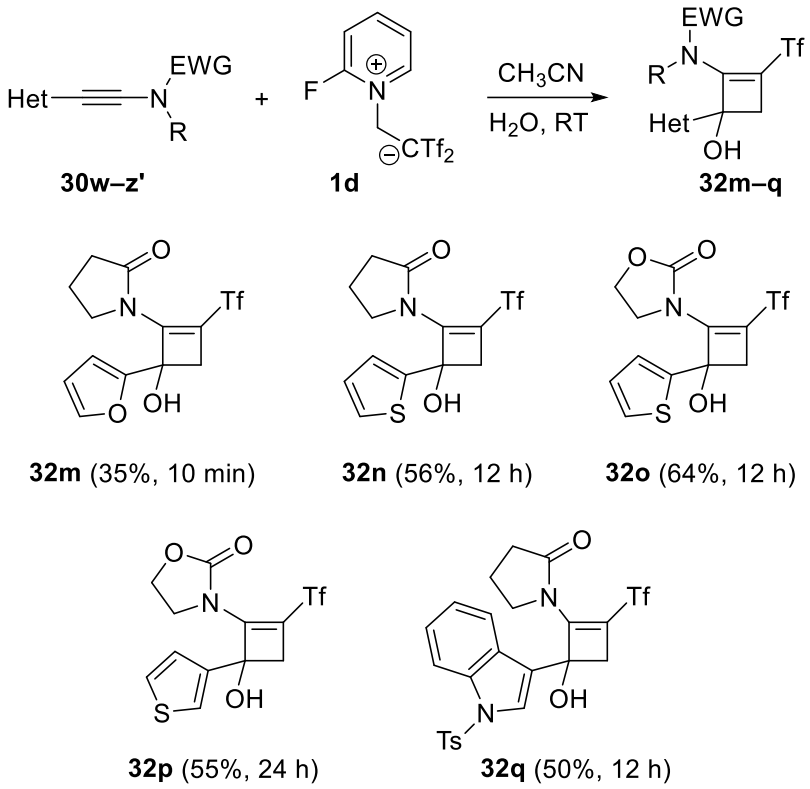


Figure VI.3. ORTEP representation of 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol **32a**. Thermal ellipsoids are shown at 50% probability.

On the basis of the structure of aminocyclobutenol **32a**, it must be assumed the participation of adventitious water. The addition of external water was not required, but the inclusion of 1.5 equivalents of H_2O accelerated the process. In view of the fact that all reported methods for accessing cyclobutenols should start from cyclobutenones, our protocol could open new horizons for the generation of cyclobutenols in a complementary selective manner by another mechanistically different strategy.

With a number of aromatic-substituted ynamides found to be compatible with the optimized reaction conditions, heteroaromatic rings were investigated to further expand the scope of the reaction (Scheme VI.4).

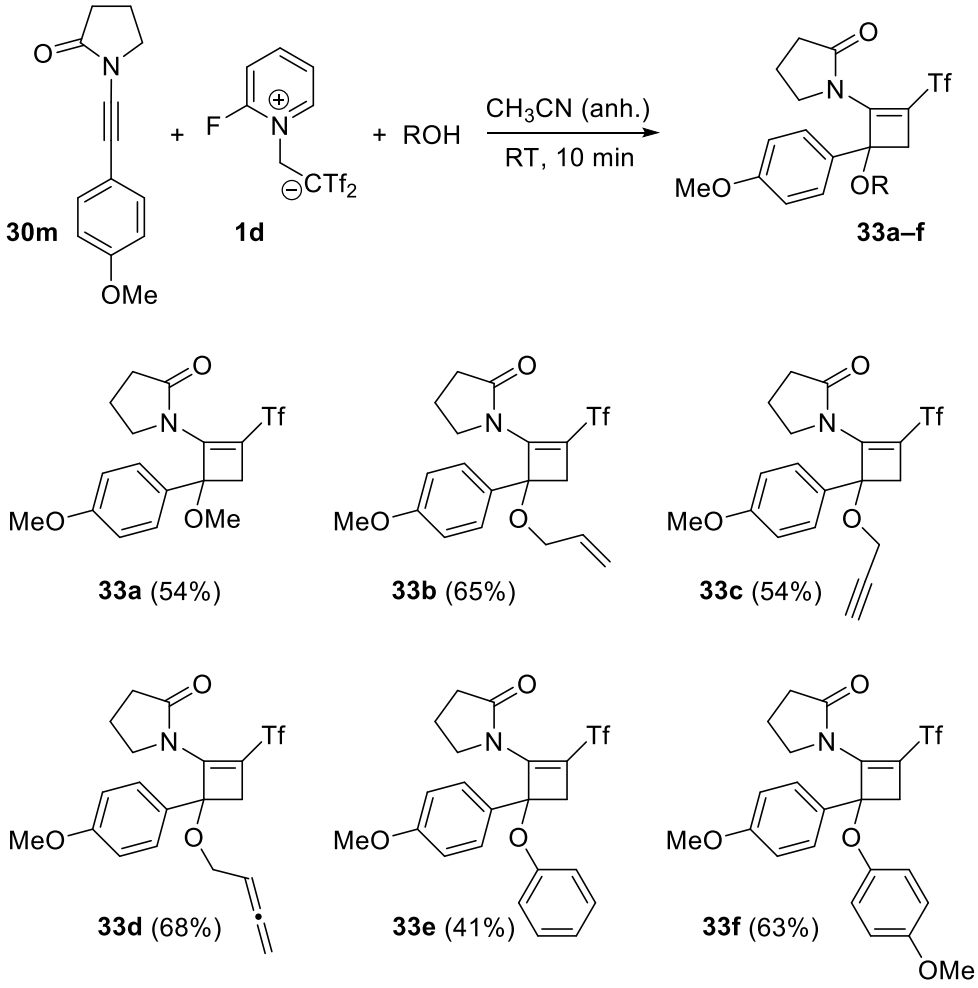


Scheme VI.5. Uncatalyzed reaction of ynamides **30** with zwitterion **1d**. Controlled synthesis of 1-hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **32.**

Ynamides bearing at the *C*-terminal several heterocycles including furan, thiophene, and indole did not reduce reactivity of the alkyne. Thus, ynamides **30w–z'** reacted with zwitterion **1d** in acetonitrile at room temperature to give aminocyclobutenols **32m–q**. Again, it seems that moderately electron-rich rings have a better performance than highly activated ones (adduct **32m**). Substrate **30z'**, with a large group flanking the ynamide, smoothly underwent the desired transformation. Electronic but not steric variation of the ynamide derivatives played a role in determining the reactivity of alkynes **30**. The absence of hydroxylated products formed from ynamides **30a–j** points to a strong activating effect of electrondonating substituents in ynamides **30k–z'**.

Since the ratio products **31** and **32** may be considered an approximate measure of the relative reactivity of the aminocyclobutene ring towards oxygenated nucleophiles, we decided to perform the reaction of ynamide **30m** with alcohols under otherwise identical conditions. The studies of aminocyclobutene formation with addition of methanol, prop-2-en-1-ol, prop-2- yn-1-ol, and propa-1,2-dien-1-ol

demonstrated that the presence of the alcohol moiety exlusively gives aminocyclobutenyl ethers **33a–d**, with the hydroxy group acting as a nucleophile (Scheme VI.5).

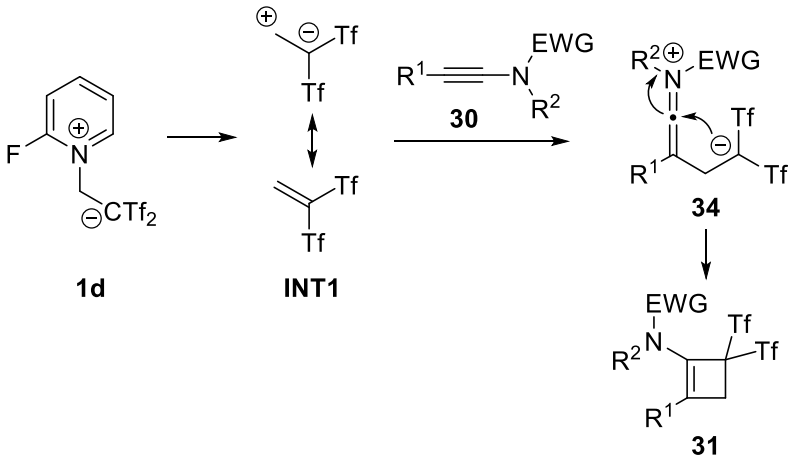


Scheme VI.5. Uncatalyzed reaction of ynamide **30m** with zwitterion **1d** in presence of alcohols. Controlled synthesis of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl) cyclobut-1-enyl pyrrolidin-2-ones **33**.

Considering the versatility of alkenes, alkynes, and allenes in chemical transformations, cyclobutenes **33b–d** are potentially interesting building blocks for further manipulation. Despite the poor nucleophilicity of phenols, they exhibit ambident reactivity because phenols bear two reaction sites, namely O and C.[10] With regards to selectivity, a major challenge with the use of phenols is to obtain exclusively aryloxylation or hydroarylation products. Interestingly, the use of phenol and mequinol resulted in the sole formation of the corresponding phenoxy derivatives

33e and **33f** (Scheme VI.5). However, the formation in 10% yield of cyclobutenol **32c** together with adduct **33e** revealed that water addition is a competitive reaction in the case of phenol but not for mequinol. It should be noted that aminocyclobutenyl ethers **33a–f** could be isolated and characterized, but they are not as stable as related aminocyclobutenols **32a–l**. The higher stability of cyclobutenols may be ascribed to hydrogen bonding, as indicated by an intramolecular O10···H19 contact in the X-ray diffraction analysis of compound **32a**.

Proposed mechanisms for the formation of aminocyclobutenes **31–33** from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl) ethan-1-ide **1d** and ynamides **30** are shown in Schemes VI.6 and VI.7. It may initially involve the formation of alkene **INT1**, which may be considered as a resonance hybrid between dipolar and uncharged species, from zwitterion **1d**. Next, the stepwise [2+2] cycloaddition reaction between ynamides **30** and the in situ-generated bis(trifluoromethylsulfonyl)ethane **INT1** should take place, initially leading to the zwitterionic species **34**. The addition product **34** initiates a ring-closing reaction to afford 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **31**. The observed exquisite regiocontrol may arise from the stabilization imparted by the amide group in intermediate **34**, which overrides the effect of the other substituent.

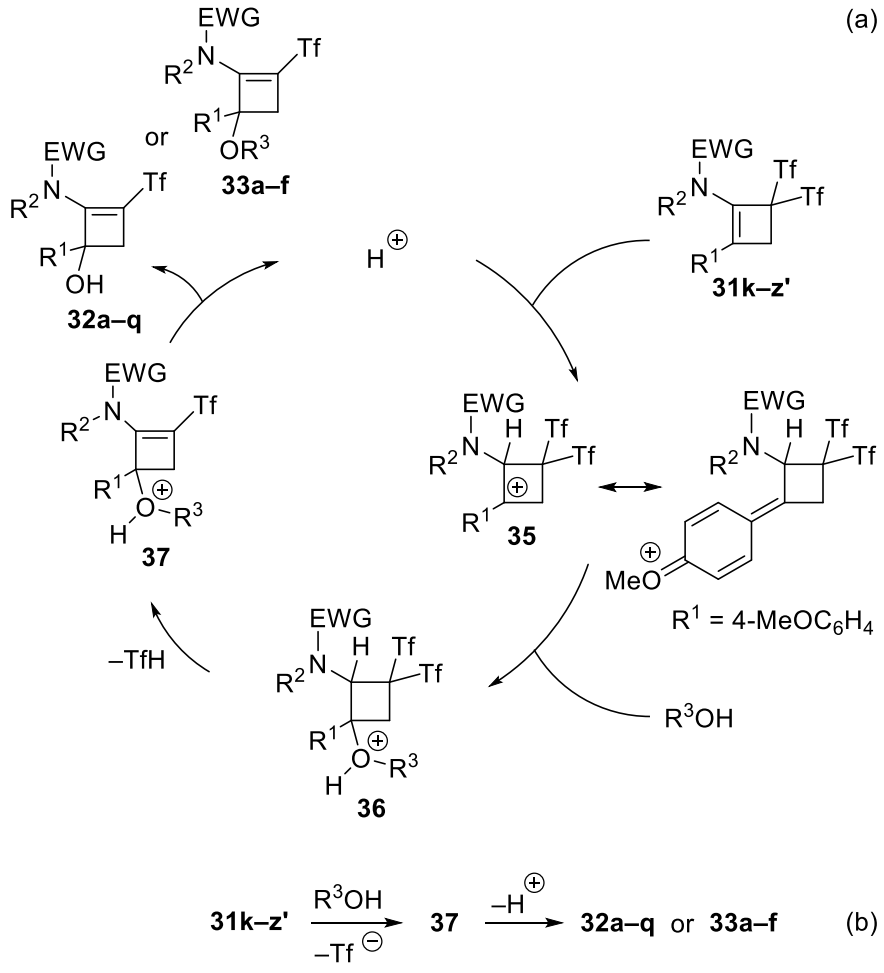


1d **INT1**

Scheme VI.6. Mechanistic explanation for the synthesis of aminocyclobutenes **31** from ynamides **30** and zwitterion **1d**.

For activated ynamides **30k–z'**, the presence of water or alcohols in the reaction media could trigger a rapid nucleophilic attack with concomitant

trifluoro(hydrosulfonyl)methane (TfH) elimination, thus leading to the final 1-aryl-2-amino-3-(trifluoromethylsulfonyl)-cyclobut-2-enols **32** or 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones **33**. The conversion of aminocyclobutenes of type **31** into adducts **32** and **33** could be catalysed by protons (Scheme VI.7a, top side).



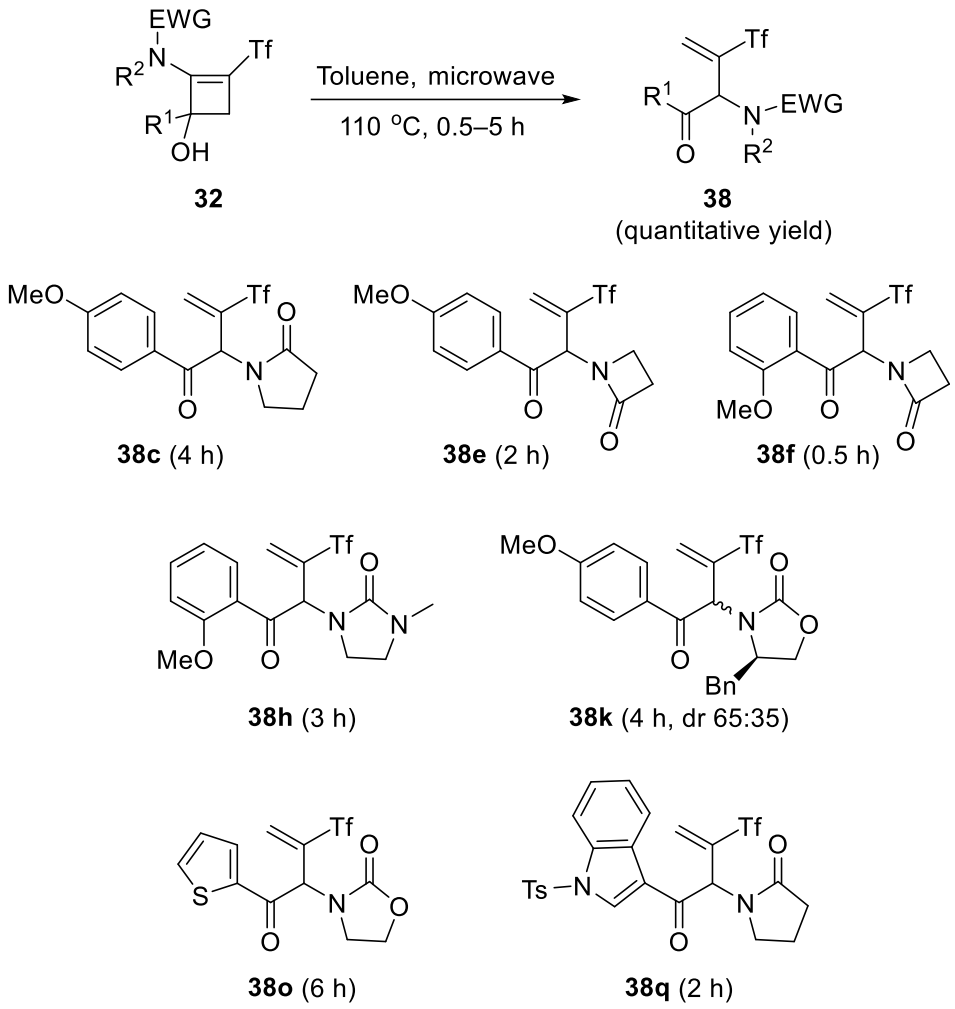
Scheme VI.7. Mechanistic explanation for the synthesis of aminocyclobutenes **32** and **33**.

A possible pathway for the formation of adducts **32** and **33** may initially involve the formation of carbocations **35** through addition of the proton to the enamine double bond in transient 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamide intermediates **31k–z'**. The driving force of this process may be related to the stabilization of the positive charge in intermediates **35** by electron-rich substituents. Next, intermolecular nucleophilic attack of the oxygen at the benzylic position of cationic species **35** would form an oxonium cation of type **36**. Subsequent loss of TfH-generated species **37**

followed by proton release afforded aminocyclobutenol derivatives **32** and **33** with concurrent regeneration of the catalyst.

The treatment of cyclobut-1-enamide **31c** with water under acidic catalysis (HCl, H_2SO_4 or TfOH) did result in complex reaction mixtures. This experimental result, combined with the unusual protonation of enamides at the α-carbon, led us to propose an alternative mechanism for the formation of cyclobutenol derivatives **32** and **33** (Scheme VI.7b, bottom side). In this way, the direct nucleophilic attack of water or alcohols into the benzylic position should produce intermediate **37** with concomitant Tf^- release.

Having developed a direct approach to aminocyclobutenol derivatives **32a–q** and **33a–f** as single isomers from ynamides, we were then interested in using the inherent ring strain[11] of these highly functionalized four-membered carbocycles to perform a selective carbon–carbon bond fragmentation as a new entry to aminoalkenes. Attempts to generate a ring-opened structure from **32c** in refluxing benzene failed. Ring opening of substrate **32c** was successfully accomplished in a microwave reactor by heating a solution of aminocyclobutenol **32c** in toluene at 110ºC (Scheme VI.8).



32

38 (quantitative yield)

38c (4 h) **38e** (2 h) **38f** (0.5 h)

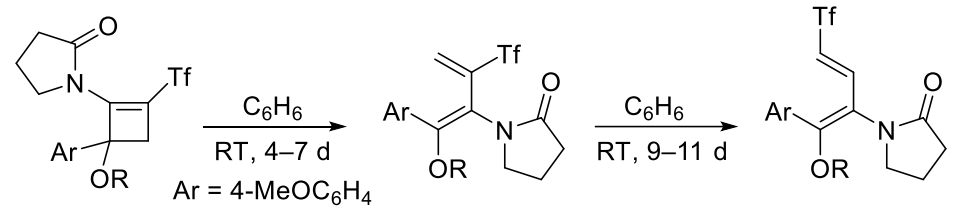
38h (3 h) **38k** (4 h, dr 65:35)

38o (6 h) **38q** (2 h)

Scheme VI.8. Ring opening of aminocyclobutenols **32**. Synthesis of 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **38**.

In this way, α-amino-β,γ-unsaturated ketone **38c** was cleanly obtained in quantitative yield. Remarkably, this rearrangement was the only operative reaction mode. Accordingly, we carried out the thermally promoted ring opening of several adducts **32** and we smoothly obtained the corresponding 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **38e**, **38f**, **38h**, **38k**, **38o**, and **38q** in quantitative yields. Enantioenriched oxazolidinone **38k** was formed as diasteromeric mixture (d.r.= 65:35) at the newly generated stereogenic center. In all these cases, we once again observed the sole formation of the β,γ-unsaturated ketone (Scheme VI.8). It should be noted that traditional strategies for the preparation of functionalized β,γ-unsaturated ketones are problematic owing to the possible isomerisation to the α, β-unsaturated ketone.

The utility of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones as precursors for further elaboration is demonstrated in Scheme VI.9. When adduct **33a** was dissolved in benzene at room temperature, the 4π-electrocyclic ring opening to place to give the (*Z*)-1-methoxy-1-aryl-3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amine derivative **39a** in good yield. Similarly, the use of compounds **33b–f** as starting materials also efficiently promoted the fragmentation. In each case, (*Z*)-1,3-dienes **39a–f** were formed with total stereoselectivity.[12] The crude reaction mixtures are extremely clean for aminocyclobutenes **33b** and **33d**, giving dienes **39b** and **39d** as the only products detected. Remarkably, the mild conditions of the rearrangement allow the selective formation of diene **39d** without harming the sensitive allene functionality (Scheme VI.9).

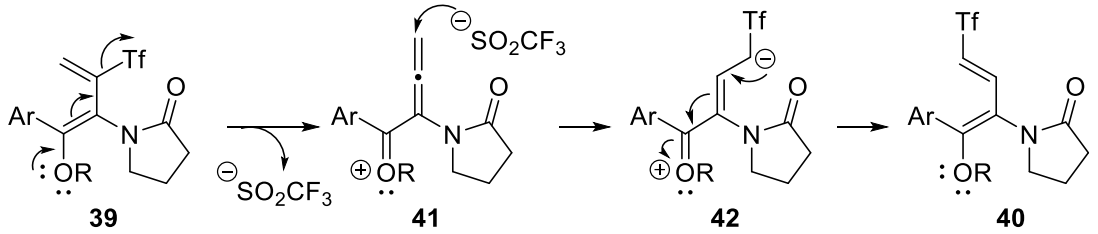


33a R = methyl	**39a** (75%)	
33b R = prop-2-enyl	**39b** (quantitative)	
33c R = prop-2-ynyl	**39c** (57%)	**40c** (51%)
33d R = buta-2,3-dienyl	**39d** (quantitative)	**40d** (38%)
33e R = phenyl	**39e** (53%)	**40e** (67%)
33f R = 4-methoxyphenyl	**39f** (48%)	**40f** (64%)

Scheme VI.9. Ring opening of alkoxycyclobutenamines 6. Synthesis of functionalized buta-1,3-dien-2-amines **39** and **40**.

Surprisingly, 3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amines **39** can undergo a further reaction in benzene solution through a spontaneous uncatalyzed migration process at room temperature to give (1*Z*,3*E*)-1-alkoxy-1-aryl-4-(trifluoromethylsulfonyl)-buta-1,3-dien-2-amines **40c–f** (Scheme VI.9). To explain the conversion of **39** into **40**, we must invoke the versatility of sulfone-type groups, which can act as both leaving groups and as nucleophiles.[13] Thus, the critical step in the formal triflyl migration of dienes **39** is the elimination of a trifluoromethanesulfinate anion to afford the allenamide intermediate **41** (Scheme VI.10). Next, nucleophilic addition of the trifluoromethanesulfinate anion to the terminal allene carbon of **41**

generates zwitterionic species **42**, which, after a final rearrangement, produces triflones **40** (Scheme VI.10).



Scheme VI.10. Mechanistic explanation for the formal triflyl migration in dienes **39**.

VI.2.3. Conclusion

In conclusion, the [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ regioselectively afforded bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with ynamides bearing electronrich aromatic rings at the *C*-terminal, an interesting reactivity switch was observed. In such cases, a cyclization/hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. The study of aminocyclobutene formation with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3-(triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

VI.3. Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or acetone-d_6 (^{1}H, 2.0 ppm; ^{13}C, 206.3 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or CD_3CN (^{1}H, 2.0 ppm; ^{13}C, 118.2 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. Microwave irradiation was carried out in a Monowave 300 from Anton Paar GmbH. The reaction temperatures during microwave heating were measured with an internal infrared sensor. All commercially available compounds were used without further purification.

General procedure for the synthesis of 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides 31a–j. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1.0 mmol) was added at room temperature to a solution of the appropriate ynamide **30a–j** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until disappearance of the starting material (instantaneous reaction), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenes **31** follow.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 4a. From 30 mg (0.16 mmol) of ynamide **3a**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **4a** (72 mg, 94%) as a colorless solid; mp 112–114 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.45 (m, 5H, CH^{Ar}), 4.52 (dd, 2H, *J* = 8.7, 7.1 Hz, CH_2), 4.07 (dd, 2H, *J* = 8.9, 6.9 Hz, CH_2), 3.53 (s, 2H, CH_2-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 154.0 (C=O), 147.8 (C=*C*-N), 131.9 (CH^{Ar}), 129.1 (*C*=C-N), 128.9 ($2CH^{Ar}$), 128.4 ($2CH^{Ar}$), 119.8 (q, J_{CF} = 331.3 Hz, $2CF_3$), 117.9 ($C^{Ar\text{-}q}$), 88.4 (CTf_2), 63.1 (CH_2), 44.8 (CH_2), 31.8 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.87 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1771 (C=O), 1669 (C=C), 1380, 1104 (O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{11}NO_6S_2F_6$ $[M]^+$: 478.9932; found: 478.9928.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31b. From 30 mg (0.17 mmol) of ynamide **30b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 90:10) as eluent gave compound **31b** (65 mg, 80%) as a colorless solid; mp 107–109 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.45 (s, 5H, CH^{Ar}), 3.86 (t, 2H, *J* = 4.7 Hz, CH_2), 3.50 (s, 2H, CH_2-*cyclobutene*), 3.20 (t, 2H, *J* = 4.7 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 164.8 (C=O), 142.0 (C=*C*-N), 131.4 (CH^{Ar}), 129.4 (*C*=C-N), 128.8 ($2CH^{Ar}$), 128.3 ($2CH^{Ar}$), 119.8 (q, J_{CF} = 331.2 Hz, $2CF_3$), 115.7 ($C^{Ar\text{-}q}$), 86.7 (CTf_2), 41.8 (CH_2), 37.6 (CH_2), 32.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.62 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1772 (C=O), 1667 (C=C), 1378, 1105 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{11}NO_5S_2F_6$ $[M]^+$: 462.9983; found: 462.9989.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31c. From 33 mg (0.18 mmol) of ynamide **30c**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 90:10) as eluent gave compound **31c** (71 mg, 84%) as a colorless solid; mp 125–127 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.46 (m, 3H, CH^{Ar}), 7.34 (m, 2H, CH^{Ar}),

3.86 (t, 2H, *J* = 7.0 Hz, CH_2), 3.53 (s, 2H, CH_2-*cyclobutene*), 2.55 (t, 2H, *J* = 8.0 Hz, CH_2), 2.22 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 173.9 (C=O), 146.2 (C=*C*-N), 131.4 (CH^{Ar}), 129.8 (*C*=C-N), 128.7 ($2CH^{Ar}$), 128.3 ($2CH^{Ar}$), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 119.4 ($C^{Ar\text{-}q}$), 88.5 (CTf_2), 47.6 (CH_2), 31.8 (CH_2), 30.5 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.92 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1727 (C=O), 1662 (C=C), 1382, 1104 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{13}NO_5S_2F_6$ $[M]^+$: 477.0139; found: 477.0159.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31d. From 20 mg (0.12 mmol) of ynamide **30d**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **31d** (54 mg, 73%) as a colorless oil; ^1H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.16 (m, 2H, $2CH^{Ar}$), 7.05 (m, 3H, $3CH^{Ar}$), 3.48 (m, 2H, CH_2), 3.11 (s, 2H, CH_2-*cyclobutene*), 2.41 (m, 2H, CH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 155.9 (C=O), 143.9 (C=*C*-N), 130.7 (CH^{Ar}), 130.6 ($C^{Ar\text{-}q}$), 128.6 ($2CH^{Ar}$), 128.5 ($2CH^{Ar}$), 121.4 (*C*=C-N), 120.5 (q, J_{CF} = 331.9 Hz, $2CF_3$), 89.4 (CTf_2), 44.2 (CH_2), 42.3 (CH_2), 31.9 (CH_2), 30.7 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.15 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1730 (C=O), 1623 (C=C), 1383, 1104 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{14}N_2O_5S_2F_6$ $[M]^+$: 492.0248; found: 492.0245.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31e. From 31 mg (0.126 mmol) of ynamide **30e**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **31e** (65 mg, 96%) as a colorless solid; mp 140–142 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 6.55 (t, 1H, *J* = 2.2 Hz, CH^{Ar}), 6.46 (d, 2H, *J* = 2.2 Hz, CH^{Ar}), 3.82 (m, 8H, CH_2 + OCH_3), 3.48 (s, 2H, CH_2-*cyclobutene*), 2.52 (t, 2H, *J* = 8.0 Hz, CH_2), 2.20 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 173.9 (C=O), 160.8 ($2C^{Ar\text{-}q}$-OCH_3), 146.6 (C=*C*-N), 131.2 (*C*=C-N), 120.1 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 106.3 ($2CH^{Ar}$), 103.3 (CH^{Ar}), 88.5 (CTf_2), 55.4 ($2OCH_3$), 47.7 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 19.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.89 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1728 (C=O), 1595 (C=C), 1382, 1104 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{17}NO_7S_2F_6$ $[M]^+$: 537.0351; found: 537.0343.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31f. From 26 mg (0.178 mmol) of ynamide **30f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **31f** (32 mg, 57%) as a colorless solid; mp 129–131 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 6.58 (t, 1H, *J* = 2.1 Hz, CH^{Ar}), 6.53 (d, 2H, *J* = 2.2 Hz, CH^{Ar}), 4.52 (t, 2H, *J* = 7.9 Hz, CH_2), 4.06 (t, 2H, *J* = 7.9 Hz, CH_2), 3.81 (m, 6H, $2OCH_3$), 3.48 (s, 2H, CH_2-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 161.0 ($2C^{Ar\text{-}q}$-OCH_3), 154.0 (C=O), 148.1 (C=*C*-N), 130.6 (*C*=C-N), 119.8 (q, J_{CF} = 331.4 Hz, $2CF_3$), 118.6 ($C^{Ar\text{-}q}$), 106.5 ($2CH^{Ar}$), 103.8 (CH^{Ar}), 88.3 (CTf_2), 63.1 (CH_2), 55.5 ($2OCH_3$), 44.9 (CH_2), 32.0 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.80 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1771 (C=O), 1592 (C=C), 1380, 1104 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}NO_8S_2F_6$ $[M]^+$: 539.0143; found: 539.0154.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31g. From 22 mg (0.178 mmol) of ynamide **30g**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10 → 85:15) as eluent gave compound **31g** (30 mg, 62%) as a yellow solid; mp 130–132 ºC; ^1H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.76 (t, 1H, *J* = 1.8 Hz, CH^{Ar}), 7.70 (m, 1H, CH^{Ar}), 6.88 (d, 1H, *J* = 7.8 Hz, CH^{Ar}), 6.69 (t, 1H, *J* = 8.0 Hz, CH^{Ar}), 3.48 (t, 2H, *J* = 7.0 Hz, CH_2), 2.93 (s, 2H, CH_2-*cyclobutene*), 1.79 (t, 2H, *J* = 8.1 Hz, CH_2), 1.19 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 173.1 (C=O), 148.2 (C=*C*-N), 140.7 ($C^{Ar\text{-}q}$), 133.5 (CH^{Ar}), 131.7 (*C*=C-N), 129.0 (CH^{Ar}), 124.8 (CH^{Ar}), 123.1 (CH^{Ar}), 122.1 ($C^{Ar\text{-}q}$), 120.3 (q, J_{CF} = 331.7 Hz, $2CF_3$), 88.4 (CTf_2), 47.6 (CH_2), 32.0 (CH_2), 30.0 (CH_2), 18.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.18 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1727 (C=O), 1660 (C=C), 1382, 1103

(O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{12}N_2O_7S_2F_6$ $[M]^+$: 521.9990; found: 521.9986.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31h. From 30 mg (0.113 mmol) of ynamide **30h**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 90:10) as eluent gave compound **31h** (65 mg, quantitative yield) as a colorless solid; mp 112–114 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.57 (m, 2H, $2CH^{Ar}$), 7.16 (m, 2H, $2CH^{Ar}$), 3.86 (t, 2H, *J* = 7.0 Hz, CH_2), 3.50 (s, 2H, CH_2-*cyclobutene*), 2.55 (t, 2H, *J* = 8.1 Hz, CH_2), 2.22 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 173.9 (C=O), 144.1 (C=*C*-N), 132.0 ($2CH^{Ar}$), 129.6 ($2CH^{Ar}$), 128.7 (*C*=C-N), 126.0 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 119.7 ($C^{Ar\text{-}q}$), 88.3 (CTf_2), 47.7 (CH_2), 31.8 (CH_2), 30.5 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –69.92 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1726 (C=O), 1660 (C=C), 1382, 1104 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{12}NO_5BrS_2F_6$ $[M]^+$: 554.9244; found: 554.9228.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31i. From 20 mg (0.12 mmol) of ynamide **30i**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 90:10) as eluent gave compound **31i** (50 mg, 91%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 3.39 (t, 2H, *J* = 7.0 Hz, CH_2), 2.70 (s, 2H, CH_2-*cyclobutene*), 2.16 (t, 2H, *J* = 6.9 Hz, CH_2), 1.75 (t, 2H, *J* = 8.1 Hz, CH_2), 1.17 (m, 6H, $3CH_2$), 0.80 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 173.3 (C=O), 150.1 (C=*C*-N), 122.6 (*C*=C-N), 120.4 (q, J_{CF} = 331.6 Hz, $2CF_3$), 87.9 (CTf_2), 47.2 (CH_2), 33.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 28.0 (CH_2), 22.7 (CH_2), 18.5 (CH_2), 13.7 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.62 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1730 (C=O), 1382, 1105 (O=S=O), 1200 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{17}NO_5S_2F_6$ $[M]^+$: 457.0452; found: 457.0458.

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 31j. From 30 mg (0.112 mmol) of ynamide **30j**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **31j** (64 mg, quantitative yield) as a colorless solid; mp 98–100 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 4.49 (dd, 2H, *J* = 8.7, 7.1 Hz, CH_2), 3.96 (dd, 2H, *J* = 8.7, 7.0 Hz, CH_2), 3.32 (s, 2H, CH_2-*cyclobutene*), 1.31 (m, 3H, 3CH), 1.11 (d, 18H, *J* = 7.2 Hz, $6CH_3$); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 161.4 (C=O), 155.8 (C=*C*-N), 137.0 (*C*=C-N), 120.9 (q, J_{CF} = 330.7 Hz, $2CF_3$), 91.9 (CTf_2), 64.0 (CH_2), 46.3 (CH_2), 35.0 (CH_2), 19.1 ($6CH_3$), 12.2 (3CH); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –70.86 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1730 (C=O), 1382, 1105 (O=S=O), 1200 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{27}NO_6S_2F_6Si$ $[M]^+$: 559.0953; found: 559.0942.

General procedure for the synthesis of 1-substituted-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols 32a–q. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1.0 mmol) and water (1.5 mmol) were sequentially added at room temperature to a solution of the appropriate ynamide **30k–z'** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenols **32** follow.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32a. From 50 mg (0.23 mmol) of ynamide **30k**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **32a** (60 mg, 64%) as a colorless solid; mp 116–118 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.32 (m, 2H, $2CH^{Ar}$), 6.91 (m, 2H, $2CH^{Ar}$), 4.58 (m, 3H, CH_2, OH), 4.36 (m, 1H, CH*H*), 4.22 (m, 1H, C*H*H), 3.82 (s, 3H,

OCH_3), 3.19 (d, 1H, *J* = 10.4 Hz, CH*H-cyclobutene*), 2.88 (d, 1H, *J* = 10.4 Hz, C*H*H-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.4 ($C^{Ar\text{-}q}$-OCH_3), 155.3 (C=O), 154.2 (C=*C*-N), 132.1 ($C^{Ar\text{-}q}$), 125.0 ($2CH^{Ar}$), 119.9 (q, J_{CF} = 325.6 Hz, CF_3), 114.2 ($2CH^{Ar}$), 101.1 (*C*=C-N), 77.8 (C^{q}-OH), 64.4 (CH_2), 55.2 (OCH_3), 45.4 (CH_2), 44.8 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.34 (s, 3F, CF_3); IR ($CHCl_3$): ν = 3483 (OH), 1770 (C=O), 1620 (C=C), 1398, 1127 (O=S=O), 1198 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_6SF_3$ [*M*]$^+$: 393.0494; found: 393.0478. CCDC 1023371 contains the supplementary crystallographic data for compound 32a in this paper (www.ccdc.cam.ac.uk/data_request/cif).

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32b. From 35 mg (0.16 mmol) of ynamide **30l**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10 → 85:15) as eluent gave compound **32b** (17 mg, 53%) as a colorless solid; mp 106–108 ºC; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.73 (dd, 1H, *J* = 7.7, 1.7 Hz, CH^{Ar}), 7.01 (td, 1H, *J* = 8.2, 1.7 Hz, CH^{Ar}), 6.86 (td, 1H, *J* = 7.6, 1.1 Hz, CH^{Ar}), 6.40 (d, 1H, *J* = 8.2 Hz, CH^{Ar}), 4.82 (s, 1H, OH), 3.29 (d, 1H, *J* = 10.1 Hz, CH*H-cyclobutene*), 3.27 (m, 2H, CH_2), 3.19 (s, 3H, OCH_3), 3.01 (d, 1H, *J* = 10.0 Hz, C*H*H-*cyclobutene*), 2.91 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 159.3 ($C^{Ar\text{-}q}$-OCH_3), 155.9 (C=O), 154.4 (C=*C*-N), 129.5 (CH^{Ar}), 129.0 ($C^{Ar\text{-}q}$), 128.0 (CH^{Ar}), 121.5 (CH^{Ar}), 120.6 (q, J_{CF} = 325.9 Hz, CF_3), 111.3 (CH^{Ar}), 101.5 (*C*=C-N), 76.7 (C^{Cq}-OH), 63.5 (CH_2), 55.1 (OCH_3), 45.0 (CH_2), 43.2 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.68 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3468 (OH), 1769 (C=O), 1624 (C=C), 1399, 1103 (O=S=O), 1200 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_6SF_3$ [*M*]$^+$: 393.0494; found: 393.0499.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32c. From 50 mg (0.23 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **32c** (63 mg, 70%) as a colorless solid; mp 99–101 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.40 (m, 2H, $2CH^{Ar}$), 6.76 (m, 2H, $2CH^{Ar}$), 5.33 (s, 1H, OH), 3.50 (m, 1H, CH*H*), 3.36 (d, 1H, *J* = 10.6 Hz, CH*H-cyclobutene*), 3.35 (m, 1H, C*H*H), 3.26 (s, 3H, OCH_3), 2.88 (d, 1H, *J* = 10.4 Hz, C*H*H-*cyclobutene*), 1.26 (m, 2H, CH_2), 0.84 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 176.5 (C=O), 159.8 ($C^{Ar\text{-}q}$-OCH_3), 157.2 (C=*C*-N), 133.5 ($C^{Ar\text{-}q}$), 125.5 ($2CH^{Ar}$), 120.8 (q, J_{CF} = 326.2 Hz, CF_3), 114.5 ($2CH^{Ar}$), 101.1 (*C*=C-N), 77.8 (C^{q}-OH), 54.8 (OCH_3), 48.7 (CH_2), 45.0 (CH_2), 29.6 (CH_2), 18.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.53 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3454 (OH), 1731 (C=O), 1604 (C=C), 1374, 1107 (O=S=O), 1192 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{16}NO_5SF_3$ [*M*]$^+$: 391.0701; found: 391.0702.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32d. From 26 mg (0.12 mmol) of ynamide **30n**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **32d** (30 mg, 64%) as a colorless solid; mp 97–99 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.84 (dd, 1H, *J* = 7.7, 1.8 Hz, CH^{Ar}), 7.01 (ddd, 1H, *J* = 8.2, 7.5, 1.8 Hz, CH^{Ar}), 6.87 (td, 1H, *J* = 7.6, 1.1 Hz, CH^{Ar}), 6.41 (dd, 1H, *J* = 8.2, 0.8 Hz, CH^{Ar}), 5.36 (s, 1H, OH), 3.64 (m, 1H, CH*H*), 3.39 (m, 1H, C*H*H), 3.35 (d, 1H, *J* = 10.1 Hz, CH*H-cyclobutene*), 3.22 (s, 3H, OCH_3), 3.05 (d, 1H, *J* = 10.2 Hz, C*H*H-*cyclobutene*), 1.26 (m, 2H, CH_2), 0.94 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 176.6 (C=O), 159.6 ($C^{Ar\text{-}q}$-OCH_3), 156.0 (C=*C*-N), 129.4 ($C^{Ar\text{-}q}$), 129.3 (CH^{Ar}), 128.2 (CH^{Ar}), 121.4 (CH^{Ar}), 120.8 (q, J_{CF} = 326.2 Hz, CF_3), 111.1 (CH^{Ar}), 102.7 (*C*=C-N), 76.5 (C^{Cq}-OH), 55.0 (OCH_3), 48.6 (CH_2), 42.8 (CH_2), 29.7 (CH_2), 18.6 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.55 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3455 (OH), 1728 (C=O), 1607 (C=C), 1376, 1108 (O=S=O), 1194 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{16}NO_5SF_3$ [*M*]$^+$: 391.0701; found: 391.0697.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32e. From 53 mg (0.18 mmol) of ynamide **30o**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **32e** (73 mg, 74%) as a colorless

solid; mp 113–115 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.38 (m, 2H, 2CH^{Ar}), 6.76 (m, 2H, 2CH^{Ar}), 4.10 (s, 1H, OH), 3.27 (s, 3H, OCH_3), 3.23 (d, 1H, *J* = 10.3 Hz, CH*H-cyclobutene*), 3.07 (m, 1H, CH*H*), 2.96 (m, 1H, C*H*H), 2.84 (d, 1H, *J* = 10.3 Hz, C*H*H-*cyclobutene*), 1.77 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 165.6 (C=O), 160.1 (*C*$^{Ar\text{-}q}$-OCH_3), 156.1 (C=*C*-N), 132.3 (C$^{Ar\text{-}q}$), 125.8 (2CH^{Ar}), 120.7 (q, J_{CF} = 325.9 Hz, CF_3), 114.5 (2CH^{Ar}), 97.1 (*C*=C-N), 77.7 (C^{Cq}-OH), 54.8 (OCH_3), 44.4 (CH_2), 42.3 (CH_2), 37.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –79.00 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3489 (OH), 1779 (C=O), 1624 (C=C), 1362, 1101 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_5SF_3$ [*M*]$^+$: 377.0545; found: 377.0552.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32f. From 30 mg (0.15 mmol) of ynamide **30p**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 1:1) as eluent gave compound **32f** (42 mg, 90%) as a colorless solid; mp 75–77 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.55 (dd, 1H, *J* = 7.7, 1.7 Hz, CH^{Ar}), 7.03 (m, 1H, CH^{Ar}), 6.84 (td, 1H, *J* = 7.6, 1.0 Hz, CH^{Ar}), 6.43 (d, 1H, *J* = 7.5 Hz, CH^{Ar}), 4.19 (s, 1H, OH), 3.25 (d, 1H, *J* = 10.2 Hz, CH*H-cyclobutene*), 3.24 (s, 3H, OCH_3), 3.14 (m, 1H, CH_2), 3.05 (d, 1H, *J* = 10.2 Hz, C*H*H-*cyclobutene*), 1.83 (t, 2H, *J* = 5.3 Hz, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 165.1 (C=O), 156.8 (C=*C*-N), 156.7 (*C*$^{Ar\text{-}q}$-OCH_3), 129.9 (C$^{Ar\text{-}q}$), 127.5 (CH^{Ar}), 120.7 (q, J_{CF} = 325.8 Hz, CF_3), 121.1 (CH^{Ar}), 111.5 (CH^{Ar}), 98.0 (*C*=C-N), 77.1 (C^{Cq}-OH), 55.0 (OCH_3), 43.3 (CH_2), 42.2 (CH_2), 37.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.99 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3499 (OH), 1785 (C=O), 1623 (C=C), 1361, 1104 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_5SF_3$ [*M*]$^+$: 377.0545; found: 377.0560.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32g. From 30 mg (0.13 mmol) of ynamide **30q**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **32g** (35 mg, 66%) as a colorless solid; mp 136–138 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.56 (m, 2H, 2CH^{Ar}), 6.77 (m, 2H, 2CH^{Ar}), 5.81 (s, 1H, OH), 3.43 (d, 1H, *J* = 9.7 Hz, CH*H-cyclobutene*), 3.33 (m, 2H, CH_2), 3.23 (s, 3H, OCH_3), 2.99 (d, 1H, *J* = 9.7 Hz, C*H*H-*cyclobutene*), 1.87 (m, 2H, CH_2), 1.81 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 159.7 (*C*$^{Ar\text{-}q}$-OCH_3), 158.7 (C=O), 154.2 (C=*C*-N), 134.4 (C$^{Ar\text{-}q}$), 125.6 (2CH^{Ar}), 121.0 (q, J_{CF} = 326.1 Hz, CF_3), 114.3 (2CH^{Ar}), 93.9 (*C*=C-N), 77.9 (C^{Cq}-OH), 54.7 (OCH_3), 44.8 (CH_2), 43.5 (CH_2), 42.4 (CH_2), 29.6 (NCH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.82 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3406 (OH), 1729 (C=O), 1620 (C=C), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}N_2O_5SF_3$ [*M*]$^+$: 406.0810; found: 406.0793.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32h. From 32 mg (0.14 mmol) of ynamide **30r**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **32h** (32 mg, 57%) as a colorless solid; mp 146–148 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.91 (dd, 1H, *J* = 7.7, 1.8 Hz, CH^{Ar}), 7.00 (td, 1H, *J* = 7.8, 1.8 Hz, CH^{Ar}), 6.90 (td, 1H, *J* = 7.5, 1.1 Hz, CH^{Ar}), 6.43 (dd, 1H, *J* = 8.1, 0.8 Hz, CH^{Ar}), 5.65 (s, 1H, OH), 3.54 (m, 1H, CH*H*), 3.42 (d, 1H, *J* = 9.6 Hz, CH*H-cyclobutene*), 3.41 (m, 1H, C*H*H), 3.31 (s, 3H, OCH_3), 3.15 (d, 1H, *J* = 9.5 Hz, C*H*H-*cyclobutene*), 2.08 (m, 1H, CH*H*), 1.93 (m, 1H, C*H*H), 1.78 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 160.6 (C=O), 156.2 (*C*$^{Ar\text{-}q}$-OCH_3), 154.7 (C=*C*-N), 130.4 (C$^{Ar\text{-}q}$), 129.1 (CH^{Ar}), 128.2 (CH^{Ar}), 121.2 (CH^{Ar}), 121.0 (q, J_{CF} = 326.1 Hz, CF_3), 111.3 (CH^{Ar}), 95.5 (*C*=C-N), 76.6 (C^{Cq}-OH), 55.2 (OCH_3), 43.7 (CH_2), 42.7 (CH_2), 42.3 (CH_2), 29.6 (NCH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.85 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3413 (OH), 1726 (C=O), 1621 (C=C), 1350, 1103 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}N_2O_5SF_3$ [*M*]$^+$: 406.0810; found: 406.0799.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32i. From 32 mg (0.13 mmol) of ynamide **30s**, and after flash chromatography of the residue using hexanes/ethyl

acetate (9:1 → 8:2) as eluent gave compound **32i** (24 mg, 43%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.77 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 6.33 (m, 2H, $2CH^{Ar}$), 5.44 (s, 1H, OH), 3.65 (m, 1H, CH*H*), 3.40 (d, 1H, *J* = 10.1 Hz, CH*H-cyclobutene*), 3.37 (m, 1H, C*H*H), 3.27 (s, 3H, OCH_3), 3.17 (s, 3H, OCH_3), 3.11 (d, 1H, *J* = 10.1 Hz, C*H*H-*cyclobutene*), 1.30 (t, 2H, *J* = 8.2 Hz, CH_2), 0.90 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 176.5 (C=O), 161.2 ($C^{Ar\text{-}q}$-OCH_3), 159.7 (C=*C*-N), 157.1 ($C^{Ar\text{-}q}$-OCH_3), 129.1 (CH^{Ar}), 121.8 ($C^{Ar\text{-}q}$), 120.8 (q, J_{CF} = 326.2 Hz, CF_3), 104.7 (CH^{Ar}), 103.0 (*C*=C-N), 99.5 (CH^{Ar}), 76.5 (C^{Cq}-OH), 54.9 (OCH_3), 54.8 (OCH_3), 48.7 (CH_2), 43.0 (CH_2), 29.8 (CH_2), 18.6 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.54 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3421 (OH), 1727 (C=O), 1608 (C=C), 1374, 1109 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{18}NO_6SF_3$ [*M*]$^{+}$: 421.0807; found: 421.0807.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32j. From 31 mg (0.125 mmol) of ynamide **30t**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 9:1) as eluent gave compound **32j** (25 mg, 46%) as a colorless solid; mp 49–51 ºC; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.66 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 6.34 (dd, 1H, *J* = 8.6, 2.4 Hz, CH^{Ar}), 6.31 (d, 1H, *J* = 2.3 Hz, CH^{Ar}), 4.87 (s, 1H, OH), 3.35 (m, 1H, CH*H*), 3.33 (d, 1H, *J* = 9.9 Hz, CH*H-cyclobutene*), 3.29 (s, 3H, OCH_3), 3.24 (m, 1H, C*H*H), 3.16 (s, 3H, OCH_3), 3.07 (d, 1H, *J* = 9.9 Hz, C*H*H-*cyclobutene*), 2.95 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 161.3 ($C^{Ar\text{-}q}$-OCH_3), 158.5 (C=*C*-N), 157.0 ($C^{Ar\text{-}q}$-OCH_3), 154.5 (C=O), 128.9 (CH^{Ar}), 121.4 ($C^{Ar\text{-}q}$), 120.7 (q, J_{CF} = 326.0 Hz, CF_3), 104.9 (CH^{Ar}), 101.6 (*C*=C-N), 99.6 (CH^{Ar}), 76.7 (C^{Cq}-OH), 63.6 (CH_2), 55.0 (OCH_3), 54.9 (OCH_3), 45.1 (CH_2), 43.4 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.69 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3487 (OH), 1769 (C=O), 1621 (C=C), 1358, 1118 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{16}NO_7SF_3$ [*M*]$^{+}$: 423.0600; found: 423.0606.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol (+)-32k. From 33 mg (0.105 mmol) of ynamide **30u**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound (+)-**32k** (36 mg, 71%) as a colorless solid; mp 133–135 ºC; $[\alpha]_D$ = +331.8 (*c* 0.7, C_6H_6); ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.41 (m, 2H, $2CH^{Ar}$), 6.99 (m, 5H, $5CH^{Ar}$), 6.75 (m, 2H, $2CH^{Ar}$), 5.35 (s, 1H, OH), 4.63 (m, 1H, N-CH), 3.33 (m, 3H, CH*H-cyclobutene,* OCH_2), 3.28 (s, 3H, OCH_3), 2.93 (t, 1H, *J* = 8.3 Hz, Ph-CH*H*), 2.89 (d, 1H, *J* = 10.5 Hz, C*H*H-*cyclobutene*), 2.00 (dd, 1H, *J* = 12.9, 11.0 Hz, Ph-C*H*H); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 160.0 ($C^{Ar\text{-}q}$-OCH_3), 155.2 (C=O), 154.2 (C=*C*-N), 134.3 ($C^{Ar\text{-}q}$), 132.3 ($C^{Ar\text{-}q}$), 129.9 ($2CH^{Ar}$), 129.1 ($2CH^{Ar}$), 127.7 (CH^{Ar}), 125.7 ($2CH^{Ar}$), 120.8 (q, J_{CF} = 326.6 Hz, CF_3), 114.6 ($2CH^{Ar}$), 102.5 (*C*=C-N), 78.8 (C^{Cq}-OH), 67.1 (OCH_2), 56.9 (OCH_3), 54.8 (NCH), 44.9 (CH_2), 37.2 (Ph-CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –77.72 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3476 (OH), 1770 (C=O), 1613 (C=C), 1362, 1121 (O=S=O), 1198 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_6SF_3$ [*M*]$^{+}$: 483.0963; found: 483.0956.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol (–)-32l. From 30 mg (0.097 mmol) of ynamide **30v**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound (–)-**32l** (31 mg, 66%; d.r. = 80:20) as a colorless solid; mp 55–57 ºC; $[\alpha]_D$ = –105.2 (*c* 1.4, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.54 (m, 2H, $2CH^{Ar}$-*minor*), 7.41 (m, 2H, $2CH^{Ar}$-*major*), 6.93 (m, 4H, $4CH^{Ar}$-*minor* + *major*), 6.85 (m, 2H, $2CH^{Ar}$-*minor*), 6.75 (m, 2H, $2CH^{Ar}$-*major*), 6.68 (m, 2H, $2CH^{Ar}$-*minor*), 6.46 (m, 2H, $2CH^{Ar}$-*minor* + *major*), 5.26 (s, 1H, OH-*major*), 5.04 (s, 1H, OH-*minor*), 4.80 (m, 1H, CH-Me), 4.75 (m, 1H, CH-Me-*minor*), 4.65 (d, 1H, *J* = 7.5 Hz, CH-Ph-*major*), 4.64 (m, 1H, CH-Ph-*minor*), 3.38 (d, 1H, *J* = 10.4 Hz, CH*H-cyclobutene-major*), 3.31 (s, 3H, OCH_3-*minor*), 3.29 (d, 1H, *J* = 10.4 Hz, CH*H-cyclobutene-minor*), 3.25 (s, 3H, OCH_3-*major*), 2.96 (d, 1H, *J* = 10.1 Hz, C*H*H-*cyclobutene-minor*), 2.86 (d, 1H, *J* = 10.4 Hz, C*H*H- *cyclobutene-major*), 0.67 (m, 3H, CH_3-*minor*), 0.66 (d, 3H, *J* = 6.5 Hz, CH_3-*major*); ^{13}C NMR (125 MHz, C_6D_6, 25

°C): δ = 161.0 (*C*$^{Ar-q}$-OCH_3-*minor*), 160.0 (*C*$^{Ar-q}$-OCH_3-*major*), 155.3 (C=O-*minor*), 155.2 (C=O-*major*), 153.6 (C=*C*-N-*major*), 153.4 (C=*C*-N-*minor*), 133.0 (C^{Ar-q}-*minor*), 132.6 (C^{Ar-q}-*major*), 132.4 (C^{Ar-q}-*major*), 132.2 (C^{Ar-q}-*minor*), 128.9 (CH^{Ar}-*minor*), 128.8 (CH^{Ar}-*major*), 128.7 (2CH^{Ar}-*minor*), 128.6 (2CH^{Ar}-*major*), 125.6 (2CH^{Ar}-*major*), 125.5 (2CH^{Ar}-*major*), 125.4 (2CH^{Ar}-*minor*), 120.9 (q, J_{CF} = 326.6 Hz, CF_3-*minor*), 120.8 (q, J_{CF} = 326.7 Hz, CF_3-*major*), 114.7 (2CH^{Ar}-*minor*), 114.6 (2CH^{Ar}-*major*), 102.5 (*C*=C-N-*major*), 99.1 (*C*=C-N-*minor*), 80.9 (CH-Ph-*minor*), 80.6 (CH-Ph-*major*), 78.7 (C^{Cq}-OH-*major*), 78.4 (C^{Cq}-OH-*minor*), 58.7 (*C*H-Me-*minor*), 56.9 (*C*H-Me-*major*), 54.8 (OCH_3-*minor*), 54.7 (OCH_3-*major*), 45.2 (CH_2-*minor*), 44.9 (CH_2-*major*), 14.3 (CH_3-*major*), 13.4 (CH_3-*minor*); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.80 (s, 3F, CF_3, *minor* + *major*); IR (CH_2Cl_2): ν = 3496 (OH), 1772 (C=O), 1616 (C=C), 1373, 1122 (O=S=O), 1198 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_6SF_3$ [*M*]$^+$: 483.0963; found: 483.0975.

1-Hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32m. From 30 mg (0.171 mmol) of ynamide **30w**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 9:1) as eluent gave compound **32m** (21 mg, 35%) as a colorless solid; mp 95–97 °C; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 6.91 (dd, 1H, *J* = 1.8, 0.8 Hz, CH^{Ar}), 6.38 (dd, 1H, *J* = 3.4, 0.8 Hz, CH^{Ar}), 5.99 (dd, 1H, *J* = 3.3, 1.8 Hz, CH^{Ar}), 5.59 (s, 1H, OH), 3.38 (m, 1H, CH*H*), 3.25 (d, 1H, *J* = 10.5 Hz, CH*H-cyclobutene*), 3.24 (m, 1H, C*H*H), 3.15 (d, 1H, *J* = 10.5 Hz, C*H*H-*cyclobutene*), 1.26 (dd, 2H, *J* = 8.9, 7.7 Hz, CH_2), 0.70 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 176.7 (C=O), 155.4 (C=*C*-N), 153.6 (C^{Ar-q}), 142.1 (CH^{Ar}), 120.7 (q, J_{CF} = 326.3 Hz, CF_3), 111.1 (CH^{Ar}), 107.7 (CH^{Ar}), 102.1 (*C*=C-N), 74.4 (C^{Cq}-OH), 48.6 (CH_2), 41.7 (CH_2), 29.6 (CH_2), 17.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.55 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3454 (OH), 1730 (C=O), 1607 (C=C), 1374, 1104 (O=S=O), 1199 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{12}NO_5SF_3$ [*M*]$^+$: 351.0388; found: 351.0378.

1-Hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32n. From 30 mg (0.15 mmol) of ynamide **30x**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **32n** (32 mg, 56%) as a colorless solid; mp 114–116 °C; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 6.91 (dd, 1H, *J* = 3.5, 1.2 Hz, CH^{Ar}), 6.76 (dd, 1H, *J* = 5.0, 1.2 Hz, CH^{Ar}), 6.64 (dd, 1H, *J* = 5.0, 3.6 Hz, CH^{Ar}), 5.81 (s, 1H, OH), 3.47 (m, 1H, CH*H*), 3.35 (d, 1H, *J* = 10.6 Hz, CH*H-cyclobutene*), 3.28 (m, 1H, C*H*H), 2.91 (d, 1H, *J* = 10.6 Hz, C*H*H-*cyclobutene*), 1.26 (m, 2H, CH_2), 0.83 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 176.7 (C=O), 156.4 (C=*C*-N), 146.4 (C^{Ar-q}), 127.4 (CH^{Ar}), 125.0 (CH^{Ar}), 123.2 (CH^{Ar}), 120.6 (q, J_{CF} = 326.3 Hz, CF_3), 101.6 (*C*=C-N), 76.2 (C^{Cq}-OH), 48.7 (CH_2), 45.5 (CH_2), 29.6 (CH_2), 18.2 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.44 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3441 (OH), 1730 (C=O), 1606 (C=C), 1373, 1110 (O=S=O), 1197 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{12}NO_4S_2F_3$ [*M*]$^+$: 367.0160; found: 367.0156.

1-Hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32o. From 32 mg (0.165 mmol) of ynamide **30y**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 85:15) as eluent gave compound **32o** (39 mg, 64%) as a colorless solid; mp 127–129 °C; ^{1}H NMR (300 MHz, CD_3CN, 25 °C): δ = 7.43 (dd, 1H, *J* = 5.0, 1.2 Hz, CH^{Ar}), 7.12 (dd, 1H, *J* = 3.6, 1.2 Hz, CH^{Ar}), 7.06 (dd, 1H, *J* = 5.0, 3.6 Hz, CH^{Ar}), 5.19 (s, 1H, OH), 4.62 (m, 2H, CH_2), 4.26 (m, 2H, CH_2), 3.23 (d, 1H, *J* = 10.1 Hz, CH*H-cyclobutene*), 2.96 (d, 1H, *J* = 10.1 Hz, C*H*H-*cyclobutene*); ^{13}C NMR (75 MHz, CD_3CN, 25 °C): δ = 156.6 (C=O), 155.7 (C=*C*-N), 146.5 (C^{Ar-q}), 128.1 (CH^{Ar}), 126.2 (CH^{Ar}), 124.0 (CH^{Ar}), 120.8 (q, J_{CF} = 325.0 Hz, CF_3), 99.4 (*C*=C-N), 76.8 (C^{Cq}-OH), 66.2 (CH_2), 46.4 (CH_2), 46.3 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 °C): δ = –79.52 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1771 (C=O), 1626 (C=C), 1363, 1096 (O=S=O), 1202 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{10}NO_5S_2F_3$ [*M*]$^+$: 368.9952; found: 368.9966.

1-Hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32p. From 36 mg (0.186 mmol) of ynamide **30z**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **32p** (37 mg, 55%) as a colorless solid; mp 125–127 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 7.43 (m, 2H, CH^{Ar}), 7.07 (dd, 1H, *J* = 4.5, 1.9 Hz, CH^{Ar}), 5.06 (s, 1H, OH), 4.68 (m, 2H, CH_2), 4.34 (m, 2H, CH_2), 3.03 (d, 1H, *J* = 10.0 Hz, CH*H-cyclobutene*), 2.80 (d, 1H, *J* = 10.0 Hz, C*H*H-*cyclobutene*); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 157.9 (C=O), 155.4 (C=*C*-N), 143.5 ($C^{Ar\text{-}q}$), 127.5 (CH^{Ar}), 125.4 (CH^{Ar}), 121.9 (CH^{Ar}), 120.9 (q, J_{CF} = 325.3 Hz, CF_3), 98.5 (*C*=C-N), 76.9 (C^{Cq}-OH), 66.1 (CH_2), 46.5 (CH_2), 45.0 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –79.66 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3481 (OH), 1765 (C=O), 1621 (C=C), 1358, 1097 (O=S=O), 1196 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{10}NO_5S_2F_3$ [*M*]$^+$: 368.9952; found: 368.9949.

1-Hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 32q. From 34 mg (0.09 mmol) of ynamide **30z'**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10 → 85:15) as eluent gave compound **32q** (25 mg, 50%) as a colorless solid; mp 138–140 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.21 (d, 2H, *J* = 8.1 Hz, CH^{Ar}), 7.83 (s, 1H, CH^{Ar}), 7.73 (d, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.64 (d, 2H, *J* = 8.3 Hz, $2CH^{Ar}$), 7.07 (m, 2H, $2CH^{Ar}$), 6.52 (d, 2H, *J* = 8.1 Hz, $2CH^{Ar}$), 5.37 (s, 1H, OH), 3.42 (m, 2H, CH_2), 3.30 (d, 1H, *J* = 10.7 Hz, CH*H-cyclobutene*), 2.91 (d, 1H, *J* = 10.7 Hz, C*H*H-*cyclobutene*), 1.64 (s, 3H, CH_3), 1.24 (m, 2H, CH_2), 0.79 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 176.7 (C=O), 156.4 (C=*C*-N), 144.8 ($C^{Ar\text{-}q}$), 136.2 ($C^{Ar\text{-}q}$), 135.6 ($C^{Ar\text{-}q}$), 129.9 ($2CH^{Ar}$), 128.1 ($C^{Ar\text{-}q}$), 126.9 ($2CH^{Ar}$), 125.4 (CH^{Ar}), 124.0 (CH^{Ar}), 123.9 (CH^{Ar}), 123.3 ($C^{Ar\text{-}q}$), 120.6 (q, J_{CF} = 326.4 Hz, CF_3), 120.3 (CH^{Ar}), 114.5 (CH^{Ar}), 101.6 (*C*=C-N), 74.8 (C^{Cq}-OH), 48.7 (CH_2), 42.6 (CH_2), 29.6 (CH_2), 21.0 (CH_3), 18.2 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.19 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 3451 (OH), 1731 (C=O), 1604 (C=C), 1372, 1132 (O=S=O), 1189 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{21}N_2O_6S_2F_3$ [*M*]$^+$: 554.0793; found: 554.0788.

General procedure for the synthesis of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones 33a–f. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.1 mmol) and the corresponding alcohol or phenol (0.15 mmol) were sequentially added at room temperature to a solution of ynamide **30m** (0.1 mmol) in acetonitrile (1 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenyl ethers **33** follow.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33a. From 20 mg (0.093 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10 → 85:15) as eluent gave compound **33a** (20 mg, 54%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.62 (m, 2H, $2CH^{Ar}$), 6.79 (m, 2H, $2CH^{Ar}$), 3.35 (t, 2H, *J* = 7.2 Hz, CH_2), 3.25 (s, 3H, OCH_3), 3.22 (d, 1H, *J* = 11.2 Hz, CH*H-cyclobutene*), 3.16 (s, 3H, OCH_3), 2.93 (d, 1H, *J* = 11.1 Hz, C*H*H-*cyclobutene*), 1.33 (m, 2H, CH_2), 0.81 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 172.1 (C=O), 159.7 (*C*$^{Ar\text{-}q}$-OCH_3), 156.4 (C=*C*-N), 130.5 ($C^{Ar\text{-}q}$), 126.9 ($2CH^{Ar}$), 120.9 (q, J_{CF} = 326.8 Hz, CF_3), 114.1 ($2CH^{Ar}$), 100.3 (*C*=C-N), 83.9 (C^{Cq}-OCH_3), 54.7 (OCH_3), 52.0 (OCH_3), 48.0 (CH_2), 41.2 (CH_2), 29.5 (CH_2), 17.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –77.85 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1761 (C=O), 1594 (C=C), 1361, 1111 (O=S=O), 1208 (C-O), 1184 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{18}NO_5SF_3$ [*M*]$^+$: 405.0858; found: 405.0866.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33b. From 30 mg (0.139 mmol) of ynamide **30m**, and after flash chromatography of the residue

using hexanes/ethyl acetate (90:10) as eluent gave compound **33b** (39 mg, 65%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.63 (m, 2H, 2CH^{Ar}), 6.78 (m, 2H, 2CH^{Ar}), 5.89 (m, 1H, C*H*=CH$_2$), 5.41 (dd, 1H, *J* = 17.2, 1.7 Hz, =CH*H*), 5.09 (dd, 1H, *J* = 10.5, 1.5 Hz, =C*H*H), 3.91 (m, 2H, CH$_2$-*allylic*), 3.36 (m, 2H, CH$_2$), 3.26 (m, 4H, OCH$_3$, CH*H*-*cyclobutene*), 2.96 (d, 1H, *J* = 11.1 Hz, C*H*H-*cyclobutene*), 1.36 (m, 2H, CH$_2$), 0.83 (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 172.2 (C=O), 159.8 (*C*$^{Ar\text{-}q}$-OCH$_3$), 156.2 (C=*C*-N), 134.7 (*C*H=CH$_2$), 130.4 (C$^{Ar\text{-}q}$), 126.9 (2CH^{Ar}), 120.9 (q, J_{CF} = 326.9 Hz, CF$_3$), 116.3 (CH=*C*H$_2$), 114.1 (2CH^{Ar}), 100.4 (*C*=C-N), 83.3 (*C*^{Cq}-OCH$_2$C=CH$_2$), 65.9 (OCH$_2$), 54.8 (OCH$_3$), 47.9 (CH$_2$), 42.0 (CH$_2$), 29.6 (CH$_2$), 17.9 (CH$_2$); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.70 (s, 3F, CF$_3$); IR (CH$_2$Cl$_2$): ν = 1761 (C=O), 1594 (C=C), 1363, 1110 (O=S=O), 1209 (C-O), 1182 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{20}NO_5SF_3$ [*M*]$^+$: 431.1014; found: 431.1020.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33c. From 30 mg (0.139 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10 → 80:20) as eluent gave compound **33c** (32 mg, 54%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.54 (m, 2H, 2CH^{Ar}), 6.75 (m, 2H, 2CH^{Ar}), 4.02 (m, 2H, CH$_2$-*propargylic*), 3.35 (m, 2H, CH$_2$), 3.34 (d, 1H, *J* = 11.4 Hz, CH*H*-*cyclobutene*), 3.25 (s, 3H, OCH$_3$), 2.92 (d, 1H, *J* = 11.2 Hz, C*H*H-*cyclobutene*), 2.03 (t, 1H, *J* = 2.4 Hz, C≡CH), 1.35 (m, 2H, CH$_2$), 0.85 (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 172.3 (C=O), 159.8 (*C*$^{Ar\text{-}q}$-OCH$_3$), 155.1 (C=*C*-N), 130.0 (C$^{Ar\text{-}q}$), 126.8 (2CH^{Ar}), 120.9 (q, J_{CF} = 326.8 Hz, CF$_3$), 114.1 (2CH^{Ar}), 100.7 (*C*=C-N), 83.8 (*C*^{Cq}-OCH$_2$C≡CH), 80.0 (*C*≡CH), 74.9 (C≡*C*H), 54.8 (OCH$_3$), 53.7 (OCH$_2$), 47.9 (CH$_2$), 42.2 (CH$_2$), 29.6 (CH$_2$), 17.9 (CH$_2$); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.61 (s, 3F, CF$_3$); IR (CH$_2$Cl$_2$): ν = 3285 (C≡C-H), 2120 (C≡C), 1760 (C=O), 1594 (C=C), 1369, 1108 (O=S=O), 1211 (C-O), 1181 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}NO_5SF_3$ [*M*]$^+$: 429.0858; found: 429.0870.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33d. From 30 mg (0.139 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 9:1) as eluent gave compound **33d** (42 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.61 (m, 2H, 2CH^{Ar}), 6.79 (m, 2H, 2CH^{Ar}), 5.34 (m, 1H, C*H*=·=CH$_2$), 4.65 (m, 2H, CH=·=C*H*$_2$), 4.11 (m, 1H, OCH*H*), 3.97 (m, 1H, OC*H*H), 3.38 (m, 2H, CH$_2$), 3.28 (m, 4H, OCH$_3$, CH*H*-*cyclobutene*), 2.95 (d, 1H, *J* = 11.2 Hz, C*H*H-*cyclobutene*), 1.38 (m, 2H, CH$_2$), 0.87 (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 209.2 (C=*C*=C), 172.3 (C=O), 159.8 (*C*$^{Ar\text{-}q}$-OCH$_3$), 156.1 (C=*C*-N), 130.6 (C$^{Ar\text{-}q}$), 126.8 (2CH^{Ar}), 120.9 (q, J_{CF} = 326.9 Hz, CF$_3$), 114.1 (2CH^{Ar}), 100.5 (*C*=C-N), 88.6 (*C*H=C=CH$_2$), 83.4 (*C*^{Cq}-OCH$_2$CH=C=CH$_2$), 76.3 (CH=C=*C*H$_2$), 63.5 (OCH$_2$), 54.8 (OCH$_3$), 48.0 (CH$_2$), 42.2 (CH$_2$), 29.6 (CH$_2$), 18.0 (CH$_2$); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.64 (s, 3F, CF$_3$); IR (CH$_2$Cl$_2$): ν = 1958 (C=C=C), 1761 (C=O), 1596 (C=C), 1365, 1112 (O=S=O), 1208 (C-O), 1185 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{20}NO_5SF_3$ [*M*]$^+$: 443.1014; found: 443.1016.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33e. From 30 mg (0.139 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 9:1) as eluent gave compound **33e** (26 mg, 41%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.62 (m, 2H, 2CH^{Ar}), 7.01 (m, 2H, 2CH^{Ar}), 6.80 (m, 3H, 3CH^{Ar}), 6.69 (m, 2H, 2CH^{Ar}), 3.36 (m, 4H, CH$_2$ + CH$_2$-*cyclobutene*), 3.20 (m, 3H, OCH$_3$), 1.24 (m, 2H, CH$_2$), 0.68 (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 171.9 (C=O), 159.9 (*C*$^{Ar\text{-}q}$-OCH$_3$), 155.9 (*C*$^{Ar\text{-}q}$-OPh), 155.3 (C=*C*-N), 129.7 (2CH^{Ar}), 128.0 (2CH^{Ar}), 122.2 (CH^{Ar}), 120.8 (q, J_{CF} = 326.8 Hz, CF$_3$), 118.0 (2CH^{Ar}), 114.1 (2CH^{Ar}), 100.3 (*C*=C-N), 83.1 (*C*^{Cq}-OPh), 54.8 (OCH$_3$), 48.0 (CH$_2$), 43.6 (CH$_2$), 29.7 (CH$_2$), 17.7 (CH$_2$); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –79.51 (s, 3F, CF$_3$); IR (CH$_2$Cl$_2$): ν = 1763 (C=O), 1595 (C=C), 1363, 1113 (O=S=O), 1210 (C-O), 1189 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_5SF_3$ [*M*]$^+$: 467.1014; found: 467.1030.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 33f. From 40 mg (0.186 mmol) of ynamide **30m**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2 → 6:4 → 1:1) as eluent gave compound **33f** (58 mg, 63%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.66 (m, 2H, 2CH^{Ar}), 6.76 (m, 4H, 4CH^{Ar}), 6.63 (m, 2H, 2CH^{Ar}), 3.47 (m, 2H, CH*H*), 3.39 (d, 1H, *J* = 10.9 Hz, CH*H*-*cyclobutene*), 3.29 (m, 3H, OCH_3), 3.27 (m, 2H, C*H*H, C*H*H-*cyclobutene*), 3.25 (m, 3H, OCH_3), 1.40 (m, 2H, CH_2), 0.80 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 172.0 (C=O), 159.9 (*C*$^{Ar\text{-}cq}$-OCH_3), 155.6 (*C*$^{Ar\text{-}q}$-OCH_3), 155.4 (C=*C*-N), 149.4 (*C*$^{Ar\text{-}q}$-O-PMP), 128.7 (*C*^{Cq}) 127.8 (2CH^{Ar}), 120.8 (q, J_{CF} = 326.8 Hz, CF_3), 119.6 (2CH^{Ar}), 114.9 (2CH^{Ar}), 114.1 (2CH^{Ar}), 100.6 (*C*=C-N), 83.5 (*C*^{Cq}-OPMP), 55.1 (OCH_3), 54.8 (OCH_3), 48.1 (CH_2), 43.3 (CH_2), 29.7 (CH_2), 17.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –77.67 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1761 (C=O), 1599 (C=C), 1367, 1107 (O=S=O), 1209 (C-O), 1184 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{22}NO_6SF_3$ [*M*]$^{+}$: 497.1120; found: 497.1130.

General procedure for the synthesis of 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones 38. A stirred solution of the appropriate aminocyclobutenol **32** (0.1 mmol) in toluene (2.0 mL) was heated at 110 ºC under microwave irradiation until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and concentrated under vacuum. Further purification was not necessary. Spectroscopic and analytical data for pure forms of compounds **38** follow.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38c. From 36 mg (0.09 mmol) of aminocyclobutenol **32c**, compound **38c** (36 mg, quantitative yield) was obtained as a green pale oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.99 (m, 2H, 2CH^{Ar}), 6.97 (m, 2H, 2CH^{Ar}), 6.95 (d, 1H, *J* = 1.9 Hz =CH*H*), 6.75 (s, 1H, CH-N), 6.55 (s, 1H, =C*H*H), 3.89 (s, 3H, OCH_3), 3.60 (m, 1H, CH*H*), 3.35 (m, 1H, C*H*H), 2.45 (m, 2H, CH_2), 2.07 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 191.1 (C=O), 175.9 (NC=O), 164.7 (*C*$^{Ar\text{-}q}$-OCH_3), 140.1 (=CH_2), 139.2 (=*C*-Tf), 131.3 (2CH^{Ar}), 126.5 (C$^{Ar\text{-}q}$), 119.6 (q, J_{CF} = 327.1 Hz, CF_3), 114.4 (2CH^{Ar}), 55.6 (OCH_3), 53.7 (CH-N), 44.8 (CH_2), 30.5 (CH_2), 18.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –77.41 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1690 (NC=O, C=O), 1601 (C=C), 1366, 1104 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{16}NO_5SF_3$ [*M*]$^{+}$: 391.0701; found: 391.0698.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38e. From 35 mg (0.09 mmol) of aminocyclobutenol **32e**, compound **38e** (35 mg, quantitative yield) was obtained as a yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.98 (m, 2H, 2CH^{Ar}), 6.57 (s, 1H, CH-N), 6.50 (m, 2H, 2CH^{Ar}), 6.35 (d, 1H, *J* = 2.2 Hz =CH*H*), 5.96 (d, 1H, *J* = 2.1 Hz =C*H*H), 3.10 (s, 3H, OCH_3), 2.92 (m, 1H, CH*H*), 2.58 (m, 1H, C*H*H), 2.29 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 189.5 (C=O), 166.4 (NC=O), 164.9 (*C*$^{Ar\text{-}q}$-OCH_3), 140.2 (=CH_2), 138.9 (=*C*-Tf), 131.5 (2CH^{Ar}), 126.7 (C$^{Ar\text{-}q}$), 120.2 (q, J_{CF} = 327.1 Hz, CF_3), 114.7 (2CH^{Ar}), 55.0 (OCH_3), 53.5 (CH-N), 38.8 (CH_2), 36.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –77.95 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1757 (NC=O), 1683 (C=O), 1600 (C=C), 1366, 1103 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_5SF_3$ [*M*]$^{+}$: 377.0545; found: 377.0535.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38f. From 35 mg (0.09 mmol) of aminocyclobutenol **32f**, compound **38f** (34 mg, quantitative yield) was obtained as a pale brown oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.93 (dd, 1H, *J* = 7.8, 1.7 Hz, CH^{Ar}), 6.98 (dd, 1H, *J* = 11.5, 4.2 Hz, CH^{Ar}), 6.66 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 6.50 (s, 1H, CH-N), 6.22 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 6.06 (s, 1H, =CH*H*), 5.68 (d, 1H, *J* = 1.9 Hz =C*H*H), 3.32 (s, 3H, OCH_3), 3.13 (dd, 1H, *J* = 8.7, 5.1 Hz, CH*H*), 2.63 (dd, 1H, *J* = 8.5, 5.2 Hz, C*H*H), 2.45 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 192.1 (C=O), 167.1 (NC=O), 158.7 (*C*$^{Ar\text{-}q}$-OCH_3), 139.9 (=*C*-Tf), 137.9 (=CH_2), 135.5 (CH^{Ar}), 131.6 (CH^{Ar}), 123.9 (C$^{Ar\text{-}q}$), 121.1 (CH^{Ar}), 120.2 (q, J_{CF} =

327.2 Hz, CF_3), 112.0 (CH^{Ar}), 59.5 (OCH_3), 55.3 (CH-N), 38.9 (CH_2), 36.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.69 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1758 (NC=O), 1680 (C=O), 1367, 1104 (O=S=O), 1210 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}NO_5SF_3$ $[M]^+$: 377.0545; found: 377.0554.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38h. From 20 mg (0.049 mmol) of aminocyclobutenol **32h**, compound **38h** (20 mg, quantitative yield) was obtained as a brown oil; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.97 (dd, 1H, *J* = 7.8, 1.8 Hz, CH^{Ar}), 6.97 (m, 1H, CH^{Ar}), 6.70 (s, 1H, CH-N), 6.66 (m, 1H, CH^{Ar}), 6.23 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 6.16 (d, 1H, *J* = 2.1 Hz, =CH*H*), 5.78 (d, 1H, *J* = 2.1 Hz, =C*H*H), 3.34 (s, 3H, OCH_3), 3.33 (m, 2H, CH_2), 2.71 (m, 1H, CH*H*), 2.61 (m, 1H, C*H*H), 2.41 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 193.9 (C=O), 160.0 (NC=O), 158.5 ($C^{Ar\text{-}q}$-OCH_3), 141.1 (=*C*-Tf), 138.0 (=CH_2), 134.9 (CH^{Ar}), 131.4 (CH^{Ar}), 125.0 ($C^{Ar\text{-}q}$), 121.0 (CH^{Ar}), 120.3 (q, J_{CF} = 327.6 Hz, CF_3), 111.9 (CH^{Ar}), 61.3 (OCH_3), 55.4 (CH-N), 44.8 (CH_2), 40.9 (CH_2) 31.0 (NCH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.37 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1706 (NC=O), 1364, 1103 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{17}N_2O_5SF_3$ $[M]^+$: 406.0810; found: 406.0803.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38k. From 28 mg (0.057 mmol) of aminocyclobutenol **32k**, compound **38k** (28 mg, quantitative yield, d.r. = 65:35) was obtained as a yellow oil; $[\alpha]_D$ = +47.2 (*c* 1.3, C_6H_6); ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.86 (m, 4H, 4CH^{Ar}-*major* + *minor*), 7.00 (m, 3H, 3CH^{Ar}-*major* + *minor*), 6.82 (dd, 2H, *J* = 7.6, 1.7 Hz, 2CH^{Ar}-*minor*), 6.75 (dd, 2H, *J* = 7.4, 1.8 Hz, 2CH^{Ar}-*major*), 6.58 (s, 1H, CH-N-*minor*), 6.57 (s, 1H, CH-N-*major*), 6.52 (m, 2H, 2CH^{Ar}-*minor*), 6.48 (m, 2H, 2CH^{Ar}-*major*), 6.42 (d, 1H, *J* = 2.2 Hz, =CH*H*-*minor*), 6.28 (s, 1H, =CH*H*-*major*), 6.27 (d, 1H, *J* = 2.7 Hz, =C*H*H-*major*), 6.10 (s, 1H, =C*H*H-*minor*), 3.76 (m, 1H, Bn-CH-*major*), 3.67 (m, 1H, Bn-CH-*minor*), 3.48 (d, 2H, *J* = 7.2 Hz, OCH_2-*major*), 3.39 (dd, 2H, *J* = 12.8, 7.7 Hz, OCH_2-*minor*), 3.12 (s, 3H, OCH_3-*minor*), 3.10 (s, 3H, OCH_3-*major*), 3.06 (m, 1H, Ph-CH*H*-*minor*), 2.94 (dd, 1H, *J* = 13.8, 4.8 Hz, Ph-CH*H*-*major*), 2.29 (dd, 1H, *J* = 13.8, 9.2 Hz, Ph-C*H*H-*major*), 2.23 (dd, 1H, *J* = 12.9, 9.9 Hz, Ph-C*H*H-*minor*); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 189.7 (C=O-*major*), 189.0 (C=O-*minor*), 164.7 (NC=O-*major*), 164.5 (NC=O-*minor*), 158.0 ($C^{Ar\text{-}q}$-OCH_3-*major*), 157.3 ($C^{Ar\text{-}q}$-OCH_3-*minor*), 143.6 (=CH_2-*major*), 142.6 (=CH_2-*minor*), 139.4 (=*C*-Tf-*major*), 138.8 (=*C*-Tf-*minor*), 136.0 ($C^{Ar\text{-}q}$-*major*), 135.6 ($C^{Ar\text{-}q}$-*major*), 131.3 (2CH^{Ar}-*major*), 131.1 (2CH^{Ar}-*minor*), 129.2 (2CH^{Ar}-*minor*), 129.1 (2CH^{Ar}-*major*), 129.0 (2CH^{Ar}-*minor*), 128.9 (2CH^{Ar}-*major*), 127.3 (CH^{Ar}-*minor*), 127.2 ($C^{Ar\text{-}q}$-*major*), 127.1 (CH^{Ar}-*major*), 120.4 (q, J_{CF} = 327.0 Hz, CF_3-*minor*), 120.3 (q, J_{CF} = 327.2 Hz, CF_3-*major*), 114.6 (2CH^{Ar}-*major*), 114.5 (2CH^{Ar}-*minor*), 67.7 (OCH_2-*minor*), 67.1 (OCH_2-*major*), 57.6 (CH-N-*minor*), 57.5 (CH-Bn-*minor*), 57.4 (CH-Bn-*major*), 57.3 (CH-N-*major*), 55.0 (2OCH_3-*major* + *minor*), 39.6 (CH_2-Ph-*minor*), 39.1 (CH_2-Ph-*major*); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.40 (s, 3F, CF_3, *major*), –77.91 (s, 3F, CF_3, *minor*); IR (CH_2Cl_2): ν = 1757 (NC=O), 1688 (C=O), 1365, 1105 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_6SF_3$ $[M]^+$: 483.0963; found: 483.0965.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38o. From 40 mg (0.108 mmol) of aminocyclobutenol **32o**, compound **38o** (40 mg, quantitative yield) was obtained as a yellow oil; ^1H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.78 (dd, 1H, *J* = 3.9, 1.0 Hz, CH^{Ar}), 6.81 (dd, 1H, *J* = 4.9, 1.0 Hz, CH^{Ar}), 6.57 (s, 1H, CH-N), 6.39 (dd, 1H, *J* = 4.9, 4.0 Hz, CH^{Ar}), 6.34 (d, 1H, *J* = 2.3 Hz, =CH*H*), 5.92 (d, 1H, *J* = 2.1 Hz =C*H*H), 3.36 (m, 2H, CH_2), 3.08 (q, 1H, *J* = 8.4 Hz, CH*H*), 2.53 (td, 1H, *J* = 8.2, 6.0 Hz, C*H*H); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 185.0 (C=O), 157.1 (NC=O), 141.0 (=CH_2), 140.7 ($C^{Ar\text{-}q}$), 138.3 (=*C*-Tf), 136.4 (CH^{Ar}), 134.7 (CH^{Ar}), 129.2 (CH^{Ar}), 120.1 (q, J_{CF} = 327.3 Hz, CF_3), 62.1 (CH_2), 55.9 (CH-N), 41.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –77.65 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1751 (NC=O), 1670 (C=O), 1363, 1098 (O=S=O), 1209 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{10}NO_5S_2F_3$ $[M]^+$: 368.9953; found: 368.9960.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 38q. From 17 mg (0.03 mmol) of aminocyclobutenol **32q**, compound **38q** (17 mg, quantitative yield) was obtained as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 8.98 (m, 1H, CH^{Ar}), 8.54 (m, 1H, CH^{Ar}), 8.13 (m, 1H, CH^{Ar}), 7.71 (d, 2H, *J* = 8.4 Hz, $2CH^{Ar}$), 7.11 (m, 2H, $2CH^{Ar}$), 6.88 (s, 1H, CH-N), 6.48 (d, 2H, *J* = 8.0 Hz, $2CH^{Ar}$), 6.43 (d, 1H, *J* = 1.9 Hz, =CH*H*), 6.14 (s, 1H, =C*H*H), 2.99 (m, 1H, CH*H*), 2.67 (m, 1H, C*H*H), 1.87 (m, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.16 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 187.7 (C=O), 174.2 (NC=O), 145.6 ($C^{Ar\text{-}q}$), 140.9 (=CH_2), 138.4 (=*C*-Tf), 135.6 ($C^{Ar\text{-}q}$), 134.8 ($C^{Ar\text{-}q}$), 134.4 (CH^{Ar}), 130.2 ($2CH^{Ar}$), 127.4 ($2CH^{Ar}$), 126.3 (CH^{Ar}), 125.3 (CH^{Ar}), 123.2 (CH^{Ar}), 120.3 (q, J_{CF} = 327.3 Hz, CF_3), 118.4 ($C^{Ar\text{-}q}$), 113.8 (CH^{Ar}), 54.2 (CH-N), 44.0 (CH_2), 30.2 (CH_2) 21.0 (CH_3), 18.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –77.59 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1683 (C=O), 1371, 1103 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{21}N_2O_6S_2F_3$ [*M*]$^+$: 554.0793; found: 554.0787.

General procedure for the synthesis of buta-1,3-dien-2-amines 39. A solution of the appropriate alkoxycyclobutenamine **33** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until disappearance of the starting material (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **39** follow.

Buta-1,3-dien-2-amine 39a. From 20 mg (0.049 mmol) of aminocyclobutenyl ether **33a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **39a** (15 mg, 75%) as a bright yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ^{o}C): δ = 7.08 (m, 2H, $2CH^{Ar}$), 6.56 (m, 2H, $2CH^{Ar}$), 6.27 (s, 1H, =CH*H*), 6.08 (s, 1H, =C*H*H), 3.59 (t, 2H, *J* = 7.1 Hz, CH_2), 3.14 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 2.08 (t, 2H, *J* = 8.1 Hz, CH_2), 1.56 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ^{o}C): δ = 175.0 (C=O), 161.0 ($C^{Ar\text{-}q}$-OCH_3), 159.1 (C=*C*-N), 142.0 (=CH_2), 140.7 (*C*=C-N), 131.5 ($2CH^{Ar}$), 123.3 ($C^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 327.8 Hz, CF_3), 114.3 ($2CH^{Ar}$), 112.0 (=*C*-Tf), 56.8 (OCH_3), 54.7 (OCH_3), 48.0 (CH_2), 30.6 (CH_2), 19.0 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –78.15 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1698 (C=O), 1606 (C=C), 1360, 1115 (O=S=O), 1209 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{18}NO_5SF_3$ [*M*]$^+$: 405.0858; found: 405.0868.

Buta-1,3-dien-2-amine 39b. From 39 mg (0.049 mmol) of aminocyclobutenyl ether **33b**, compound **39b** (39 mg, quantitative yield) was obtained as a bright yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.12 (m, 2H, $2CH^{Ar}$), 6.56 (m, 2H, $2CH^{Ar}$), 6.29 (s, 1H, =CH*H*), 6.13 (s, 1H, =C*H*H), 5.66 (m, 1H, CH_2CH=CH_2), 5.08 (dd, 1H, *J* = 17.2, 1.6 Hz, CH_2CH=CH*H*), 4.98 (dd, 1H, *J* = 10.5, 1.4 Hz, CH_2CH=C*H*H), 3.89 (m, 2H, CH_2CH=CH_2), 3.66 (t, 2H, *J* = 7.0 Hz, CH_2), 3.16 (s, 3H, OCH_3), 2.08 (t, 2H, *J* = 8.0 Hz, CH_2), 1.58 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 175.1 (C=O), 161.0 ($C^{Ar\text{-}q}$-OCH_3), 158.3 (C=*C*-N), 142.2 (=CH_2), 140.5 (*C*=C-N), 133.5 (CH_2CH=CH2), 131.6 ($2CH^{Ar}$), 123.5 ($C^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 328.0 Hz, CF_3), 117.4 (CH_2CH=CH_2), 114.2 ($2CH^{Ar}$), 112.4 (=*C*-Tf), 70.3 (OCH_2), 54.8 (OCH_3), 48.3 (CH_2), 30.6 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ^{o}C): δ = –78.14 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1699 (C=O), 1603 (C=C), 1360, 1115 (O=S=O), 1210 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{20}NO_5SF_3$ [*M*]$^+$: 431.1014; found: 431.1013.

Buta-1,3-dien-2-amine 39c. From 32 mg (0.074 mmol) of aminocyclobutenyl ether **33c**, and after flash chromatography of the residue using hexanes/ethyl acetate (80:20 → 70:30) as eluent gave compound **39c** (18 mg, 57%) as a bright yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 ^{o}C): δ = 7.12 (m, 2H, $2CH^{Ar}$), 6.54 (m, 2H, $2CH^{Ar}$), 6.26 (s, 1H, =CH*H*), 6.09 (s, 1H, =C*H*H), 3.94 (d, 2H, *J* = 2.4 Hz, CH_2C≡CH), 3.77 (t, 2H, *J* = 7.1 Hz, CH_2), 3.13 (s, 3H, OCH_3), 2.06 (t, 2H, *J* = 8.1 Hz, CH_2), 2.02 (t, 1H, *J* = 2.4 Hz, ≡CH), 1.60 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ^{o}C): δ = 175.1 (C=O), 161.1 ($C^{Ar\text{-}q}$-OCH_3), 156.9 (C=*C*-N), 142.5 (=CH_2), 140.3

(*C*=C-N), 131.7 (2CH^{Ar}), 122.5 (C$^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 327.9 Hz, CF_3), 114.6 (=*C*-Tf), 114.3 (2CH^{Ar}), 78.3 (*C*≡CH), 76.2 (C≡*C*H), 56.8 (OCH_2), 54.7 (OCH_3), 48.7 (CH_2), 30.6 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.15 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1697 (C=O), 1605 (C=C), 1361, 1114 (O=S=O), 1210 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}NO_5SF_3$ [*M*]$^+$: 429.0858; found: 429.0852.

Buta-1,3-dien-2-amine 39d. From 42 mg (0.094 mmol) of aminocyclobutenyl ether **33d**, compound **39d** (42 mg, quantitative yield) was obtained as a pale yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.10 (m, 2H, 2CH^{Ar}), 6.56 (m, 2H, 2CH^{Ar}), 6.29 (s, 1H, =CH*H*), 6.12 (s, 1H, =C*H*H), 5.09 (m, 1H, C*H*=·=CH_2), 4.57 (t, 1H, *J* = 2.5 Hz, CH=·=CH*H*), 4.54 (t, 1H, *J* = 2.5 Hz, CH=·=C*H*H), 3.99 (t, 2H, *J* = 2.5 Hz, OCH*H*), 3.96 (t, 2H, *J* = 2.5 Hz, OC*H*H), 3.69 (t, 2H, *J* = 7.0 Hz, CH_2), 3.17 (s, 3H, OCH_3), 2.08 (t, 2H, *J* = 8.1 Hz, CH_2), 1.60 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 209.2 (C=*C*=C), 175.0 (C=O), 161.0 (*C*$^{Ar\text{-}q}$-OCH_3), 158.0 (C=*C*-N), 142.2 (=CH_2), 140.5 (*C*=C-N), 131.6 (2CH^{Ar}), 123.3 (C$^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 327.8 Hz, CF_3), 114.2 (2CH^{Ar}), 112.7 (=*C*-Tf), 87.5 (*C*H=C=CH_2), 76.6 (CH=C=*C*H_2), 67.2 (OCH_2), 54.8 (OCH_3), 48.3 (CH_2), 30.6 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.16 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1957 (C=C=C), 1696 (C=O), 1604 (C=C), 1360, 1113 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{20}NO_5SF_3$ [*M*]$^+$: 443.1014; found: 443.1006.

Buta-1,3-dien-2-amine 39e. From 26 mg (0.05 mmol) of aminocyclobutenyl ether **33e**, and after flash chromatography of the residue using hexanes/ethyl acetate (80:20 → 70:30) as eluent gave compound **39e** (14 mg, 53%) as a bright yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.34 (m, 2H, 2CH^{Ar}), 6.97 (m, 4H, 4CH^{Ar}), 6.69 (m, 1H, CH^{Ar}), 6.45 (m, 2H, 2CH^{Ar}), 6.35 (s, 1H, =CH*H*), 6.23 (s, 1H, =C*H*H), 3.56 (t, 2H, *J* = 7.1 Hz, NCH_2), 3.01 (s, 3H, OCH_3), 1.89 (t, 2H, *J* = 8.1 Hz, CH_2), 1.34 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 175.2 (C=O), 160.9 (*C*$^{Ar\text{-}q}$-OCH_3), 155.9 (C=*C*-N), 154.6 (*C*$^{Ar\text{-}q}$-O-C=), 143.0 (=CH_2), 140.4 (*C*=C-N), 131.6 (2CH^{Ar}), 129.8 (2CH^{Ar}), 124.0 (C$^{Ar\text{-}q}$), 123.5 (CH^{Ar}), 120.4 (q, J_{CF} = 327.6 Hz, CF_3), 118.2 (2CH^{Ar}), 117.2 (=*C*-Tf), 114.3 (2CH^{Ar}), 54.6 (OCH_3), 48.4 (CH_2), 30.6 (CH_2), 18.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –79.50 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1703 (C=O), 1600 (C=C), 1361, 1109 (O=S=O), 1208 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_5SF_3$ [*M*]$^+$: 467.1014; found: 467.1009.

Buta-1,3-dien-2-amine 39f. From 58 mg (0.11 mmol) of aminocyclobutenyl ether **33f**, and after flash chromatography of the residue using hexanes/ethyl acetate (80:20) as eluent gave compound **39f** (28 mg, 48%) as a bright yellow oil; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.34 (m, 2H, 2CH^{Ar}), 6.90 (m, 2H, 2CH^{Ar}), 6.54 (m, 2H, 2CH^{Ar}), 6.48 (m, 2H, 2CH^{Ar}), 6.36 (s, 1H, =CH*H*), 6.25 (s, 1H, =C*H*H), 3.64 (t, 2H, *J* = 7.1 Hz, CH_2), 3.12 (s, 3H, OCH_3), 3.01 (s, 3H, OCH_3), 1.95 (t, 2H, *J* = 8.1 Hz, CH_2), 1.42 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 175.2 (C=O), 160.9 (*C*$^{Ar\text{-}q}$-OCH_3), 156.1 (*C*$^{Ar\text{-}q}$-OCH_3), 155.3 (C=*C*-N), 149.4 (*C*$^{Ar\text{-}q}$-O-C=), 142.8 (=CH_2), 140.5 (*C*=C-N), 131.8 (2CH^{Ar}), 124.1 (C$^{Ar\text{-}q}$), 120.5 (q, J_{CF} = 327.8 Hz, CF_3), 119.5 (2CH^{Ar}), 116.5 (=*C*-Tf), 114.9 (2CH^{Ar}), 114.2 (2CH^{Ar}), 54.9 (OCH_3), 54.6 (OCH_3), 48.4 (CH_2), 30.4 (CH_2), 18.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.11 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1701 (C=O), 1606 (C=C), 1362, 1110 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{22}NO_6SF_3$ [*M*]$^+$: 497.1120; found: 497.1127.

General procedure for the synthesis of buta-1,3-dien-2-amines 40. A solution of the appropriate buta-1,3-dien-2-amine **39** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until disappearance of the starting material (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **40** follow.

Buta-1,3-dien-2-amine 40c. From 20 mg (0.022 mmol) of buta-1,3-dien-2-amine **39c**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2 → 7:3) as eluent gave compound **40c** (5.1 mg, 51%) as a bright yellow oil; ^{1}H NMR (700 MHz, C_6D_6, 25 ºC): δ = 7.65 (d, 1H, *J* = 14.6 Hz, Tf-CH=C*H*), 6.98 (m, 1H, CH^{Ar}), 6.48 (m, 2H, $2CH^{Ar}$), 6.20 (d, 1H, *J* = 14.6 Hz, Tf-C*H*=CH), 4.06 (s, 2H, CH_2C≡CH), 3.07 (s, 3H, OCH_3), 2.98 (t, 2H, *J* = 6.8 Hz, CH_2), 2.03 (t, 2H, *J* = 7.6 Hz, CH_2), 1.98 (t, 1H, *J* = 2.4 Hz, CH_2C≡C*H*), 1.31 (m, 2H, CH_2); ^{13}C NMR (175 MHz, C_6D_6, 25 ºC): δ = 174.2 (C=O), 167.2 (C=*C*-N) 162.5 ($C^{Ar\text{-}q}$-OCH_3), 150.1 (Tf-CH=*C*H), 132.1 ($2CH^{Ar}$), 121.5 (*C*=C-N), 120.7 (q, J_{CF} = 324.9 Hz, CF_3), 118.5 ($C^{Ar\text{-}q}$), 114.6 ($2CH^{Ar}$), 112.5 (Tf-*C*H=CH), 78.2 (CH_2*C*≡CH), 76.2 (CH_2C≡*C*H), 58.7 (OCH_3), 54.8 (*C*H_2C≡CH), 47.2 (CH_2), 30.4 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –79.62 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1697 (C=O), 1582 (C=C), 1357, 1115 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}NO_5SF_3$ [*M*]$^+$: 429.0858; found: 429.0852.

Buta-1,3-dien-2-amine 40d. From 42 mg (0.094 mmol) of buta-1,3-dien-2-amine **39d**, and after flash chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent gave compound **40d** (16 mg, 38%) as a bright yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.68 (d, 1H, *J* = 14.6 Hz, Tf-CH=C*H*), 6.98 (m, 2H, $2CH^{Ar}$), 6.52 (m, 2H, $2CH^{Ar}$), 6.21 (d, 1H, *J* = 14.6 Hz, Tf-C*H*=CH), 5.18 (m, 1H, C*H*=·=CH_2), 4.49 (m, 2H, CH=·=CH_2), 4.07 (m, 2H, OCH_2), 3.11 (s, 3H, OCH_3), 3.02 (t, 2H, *J* = 6.9 Hz, CH_2), 2.06 (t, 2H, *J* = 8.0 Hz, CH_2), 1.37 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 209.6 (C=*C*=C), 174.2 (C=O), 168.5 (C=*C*-N), 162.3 ($C^{Ar\text{-}q}$-OCH_3), 150.5 (Tf-CH=*C*H), 132.0 ($2CH^{Ar}$), 122.2 ($C^{Ar\text{-}q}$), 120.8 (q, J_{CF} = 325.4 Hz, CF_3), 117.7 (*C*=C-N), 114.5 ($2CH^{Ar}$), 111.2 (=*C*-Tf), 87.4 (*C*H=C=CH_2), 76.5 (CH=C=*C*H_2), 69.4 (OCH_2), 54.8 (OCH_3), 47.1 (CH_2), 30.5 (CH_2), 19.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –79.71 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1955 (C=C=C), 1696 (C=O), 1578 (C=C), 1357, 1116 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{20}NO_5SF_3$ [*M*]$^+$: 443.1014; found: 443.1000.

Buta-1,3-dien-2-amine 40e. From 14 mg (0.029 mmol) of buta-1,3-dien-2-amine **39e**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2 → 7:3) as eluent gave compound **40e** (9.4 mg, 67%) as a bright yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.91 (d, 1H, *J* = 14.7 Hz, Tf-CH=C*H*), 7.13 (m, 2H, $2CH^{Ar}$), 6.96 (m, 2H, $2CH^{Ar}$), 6.87 (m, 2H, $2CH^{Ar}$), 6.65 (m, 1H, CH^{Ar}), 6.42 (m, 2H, $2CH^{Ar}$), 6.32 (d, 1H, *J* = 14.7 Hz, Tf-C*H*=CH), 2.95 (s, 5H, OCH_3, CH_2), 1.85 (t, 2H, *J* = 8.0 Hz, CH_2), 1.20 (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 174.0 (C=O), 165.0 (C=*C*-N) 162.4 ($C^{Ar\text{-}q}$-OCH_3), 156.3 ($C^{Ar\text{-}q}$-O-C=), 150.0 (Tf-CH=*C*H), 132.9 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 124.3 (CH^{Ar}), 123.2 ($C^{Ar\text{-}q}$), 120.8 (q, J_{CF} = 324.7 Hz, CF_3), 119.6 ($2CH^{Ar}$), 119.2 (*C*=C-N), 114.4 ($2CH^{Ar}$), 113.5 (Tf-*C*H=CH), 54.7 (OCH_3), 46.8 (CH_2), 30.1 (CH_2), 18.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.12 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1705 (C=O), 1580 (C=C), 1358, 1117 (O=S=O), 1205 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{20}NO_5SF_3$ [*M*]$^+$: 467.1014; found: 467.1019.

Buta-1,3-dien-2-amine 40f. From 34 mg (0.068 mmol) of buta-1,3-dien-2-amine **39f**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **40f** (23 mg, 64%) as a yellow solid; mp 131–133 ºC; ^{1}H NMR (500 MHz, C_6D_6, 25 ºC): δ = 7.91 (d, 1H, *J* = 14.7 Hz, Tf-CH=C*H*), 7.16 (m, 2H, $2CH^{Ar}$), 6.93 (m, 2H, $2CH^{Ar}$), 6.49 (m, 2H, $2CH^{Ar}$), 6.44 (m, 2H, $2CH^{Ar}$), 6.31 (d, 1H, *J* = 14.7 Hz, Tf-C*H*=CH), 3.06 (s, 3H, OCH_3), 3.01 (t, 2H, *J* = 6.9 Hz, CH_2), 2.97 (s, 3H, OCH_3), 1.90 (t, 2H, *J* = 8.0 Hz, CH_2), 1.25 (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 ºC): δ = 174.1 (C=O), 166.0 (C=*C*-N) 162.3 ($C^{Ar\text{-}q}$-OCH_3), 156.6 ($C^{Ar\text{-}q}$-OCH_3), 150.3 (Tf-CH=*C*H), 149.8 ($C^{Ar\text{-}q}$-O-C=), 132.9 ($2CH^{Ar}$), 123.2 ($C^{Ar\text{-}q}$), 120.9 ($2CH^{Ar}$), 120.8 (q, J_{CF} = 325.4 Hz, CF_3), 118.9 (*C*=C-N), 114.7 ($2CH^{Ar}$), 114.3 ($2CH^{Ar}$), 112.9 (Tf-*C*H=CH), 54.9 (OCH_3), 54.6 (OCH_3), 46.9 (CH_2), 30.2 (CH_2), 18.9 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –79.54 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1707 (C=O), 1605 (C=C), 1359, 1115 (O=S=O), 1196 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{22}NO_6SF_3$ [*M*]$^+$: 497.1120; found: 497.1132.

VI.4. Notes and references

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VII. CAPÍTULO 4

VII.1. Convenient Access to 2,3-Disubstituted-cyclobut-2-en-1-ones under Suzuki Conditions and their Synthetic Utility

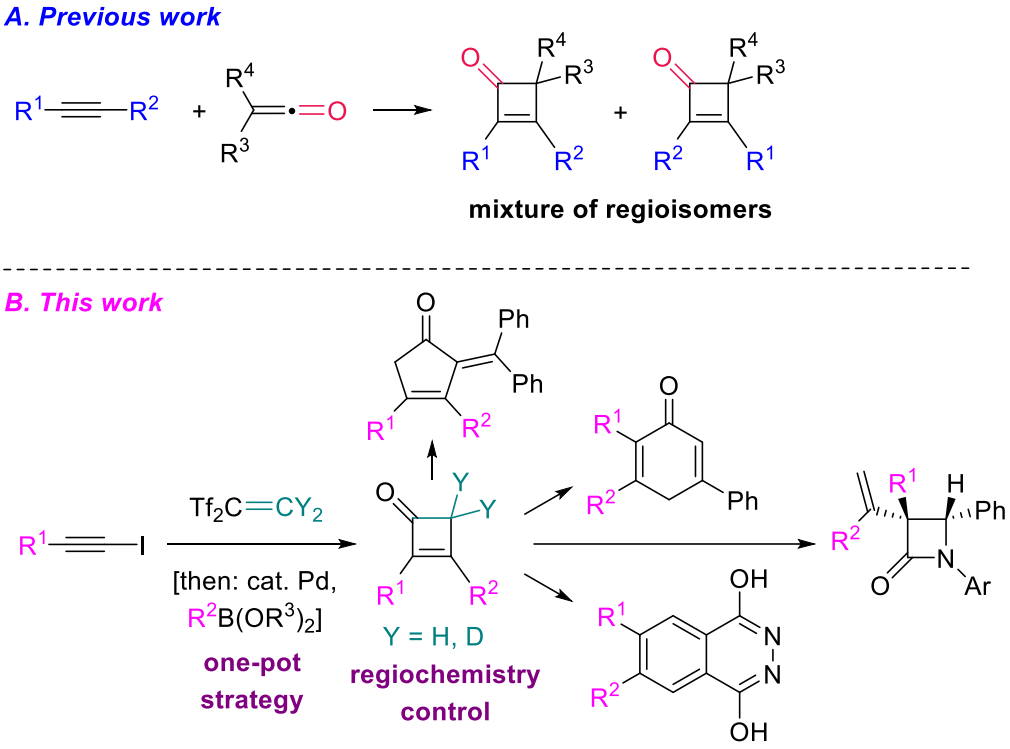
A regioselective synthesis of general applicability has been designed for the one-pot preparation of 2,3-disubstituted-cyclobutenones from yodoalkynes through cyclobutenylation, Suzuki C–C coupling reaction, and ketone formation. This one-pot methodology has been applied to the selective synthesis of an orally active cyclooxygenase II inhibitor. Besides, the obtained cyclobut-2-en-1-ones were used as useful synthons in several transformations such as for the preparation of β-lactams, phthalazines, cyclohexa-2,5-dien-1-ones, and cyclopent-3-en-1-ones.

Chem. Eur. J. **2019**, *25*, 7547

VII.2. Article

VII.2.1. Introduction

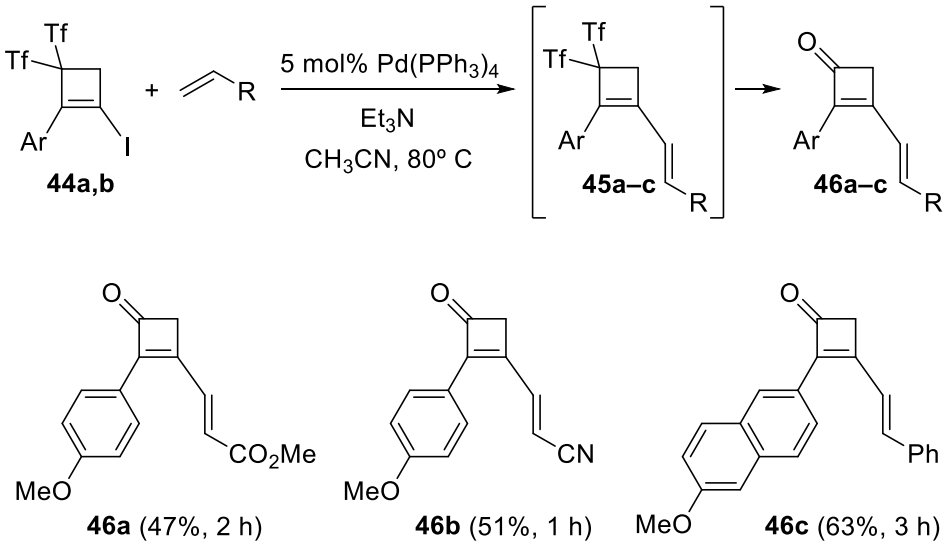
The cyclobut-2-en-1-one motif is present in several natural products such as in alterbrassicene A, which displayed enzimatic inhibitor activity.[1] In addition, the relevance of cyclobutenones as synthetic intermediates has been broadly identified in organic synthesis because ring cleavage of the four-membered carbocycle is enhanced by ring strain.[2] The classical method for the synthesis of the cyclobutenone skeleton takes advantage of the [2+2] cycloaddition reaction between alkynes and in situ-generated ketenes (Scheme VII.1A).[3] However, regioselectivity challenges may occur and isomers may be generated during the ring formation reaction. Consequently, novel methods for the controlled synthesis of cyclobutenones are highly desirable. Herein we present a one-pot synthesis of cyclobutenones from yodoalkynes through sequential bis(triflyl)cyclobutenylation and Suzuki reaction with concomitant ketone formation (Scheme VII.1B). This procedure revealed exquisite regioselectivity, offering a complement to the state-of-the-art of the available methodology. Besides, the obtained 2,3-disubstituted-cyclobut-2-en-1-ones were used as useful synthons in several transformations (Scheme VII.1B), such as the preparation of a selective an orally active cyclooxygenase II inhibitor.



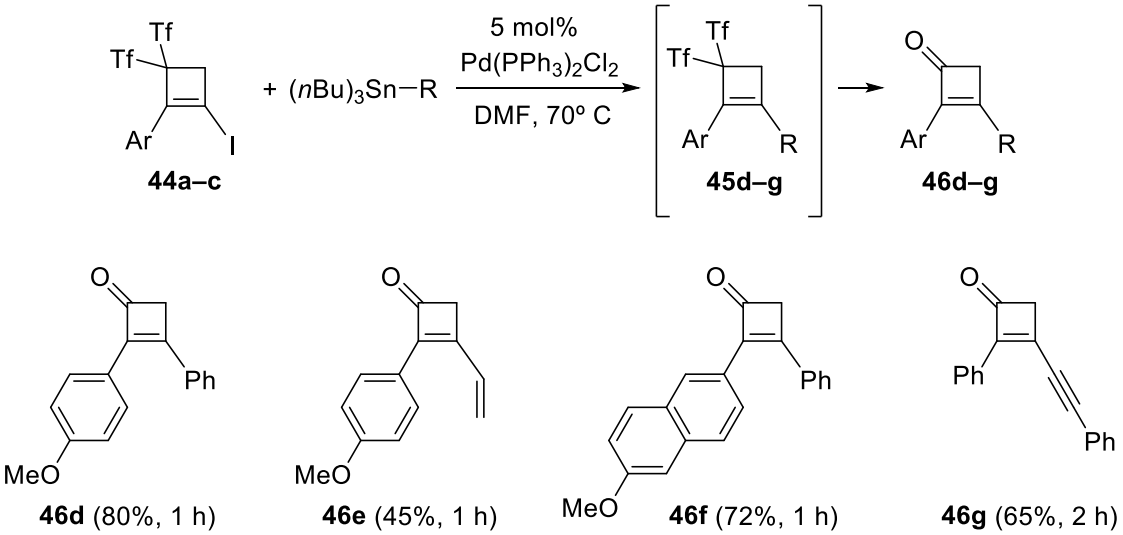
Scheme VII.1. Known methodology and current synthetic route towards the cyclobutenone motif, and associated synthetic utility.

VII.2.2. Results and discussion

We have recently described the facile synthesis of bis(triflyl)iodocyclobutenes **44** through the reaction of iodoalkynes **43** and Yanai's reagent **1d**.[4,5] We decided to set up conditions for the cross-coupling reactions of readily available adducts **44**, which should functionalizate the cyclobutene core[6] and may allow a further ketone formation. This protocol should provide a regiocontrolled access to the 2,3-disubstituted-cyclobut-2-en-1-one scaffold through the use of the bis(triflyl)methane moiety as a masked ketone. With the aim to validate our strategy, Pd-catalyzed conditions were applied for the C–C coupling of bis(triflyl)iodocyclobutenes **44**. Unfortunately, iodocyclobutenes **44** kept unreactive under Negishi conditions. Interestingly, Heck and Stille reactions proceeded well (Scheme VII.2 and Scheme VII.3). Noteworthy, concurrent ketone formation was observed to deliver 2,3-disubstituted-cyclobut-2-en-1-ones **46**, which should imply the participation of adventitious water in the hydrolysis step of the non-isolable bis(triflyl)cyclobutenes **45**.



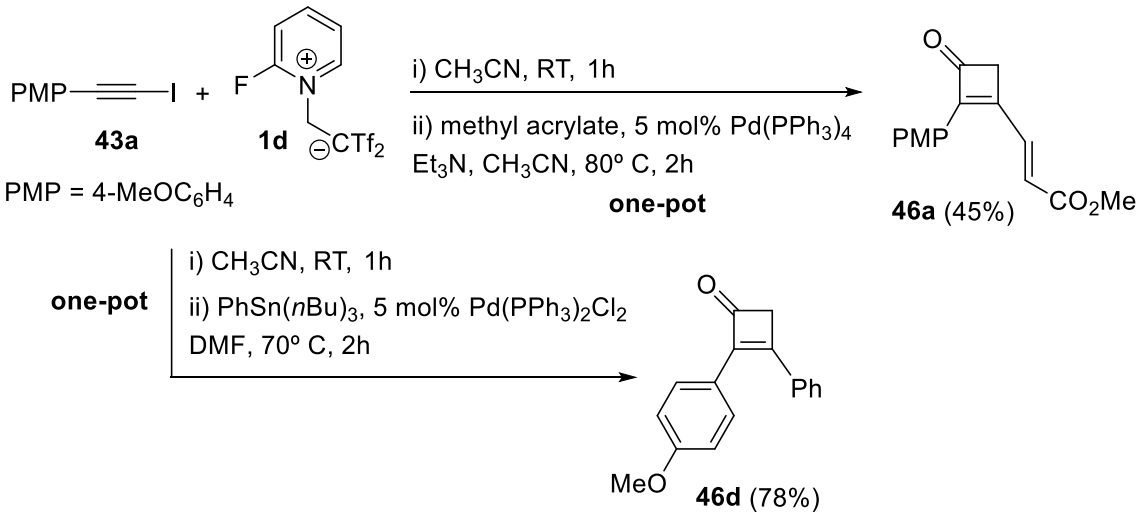
Scheme VII.2. Palladium-catalyzed reaction of bis(triflyl)iodocyclobutenes **44a,b** with alkenes. Regiocontrolled synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones **46a–c**.



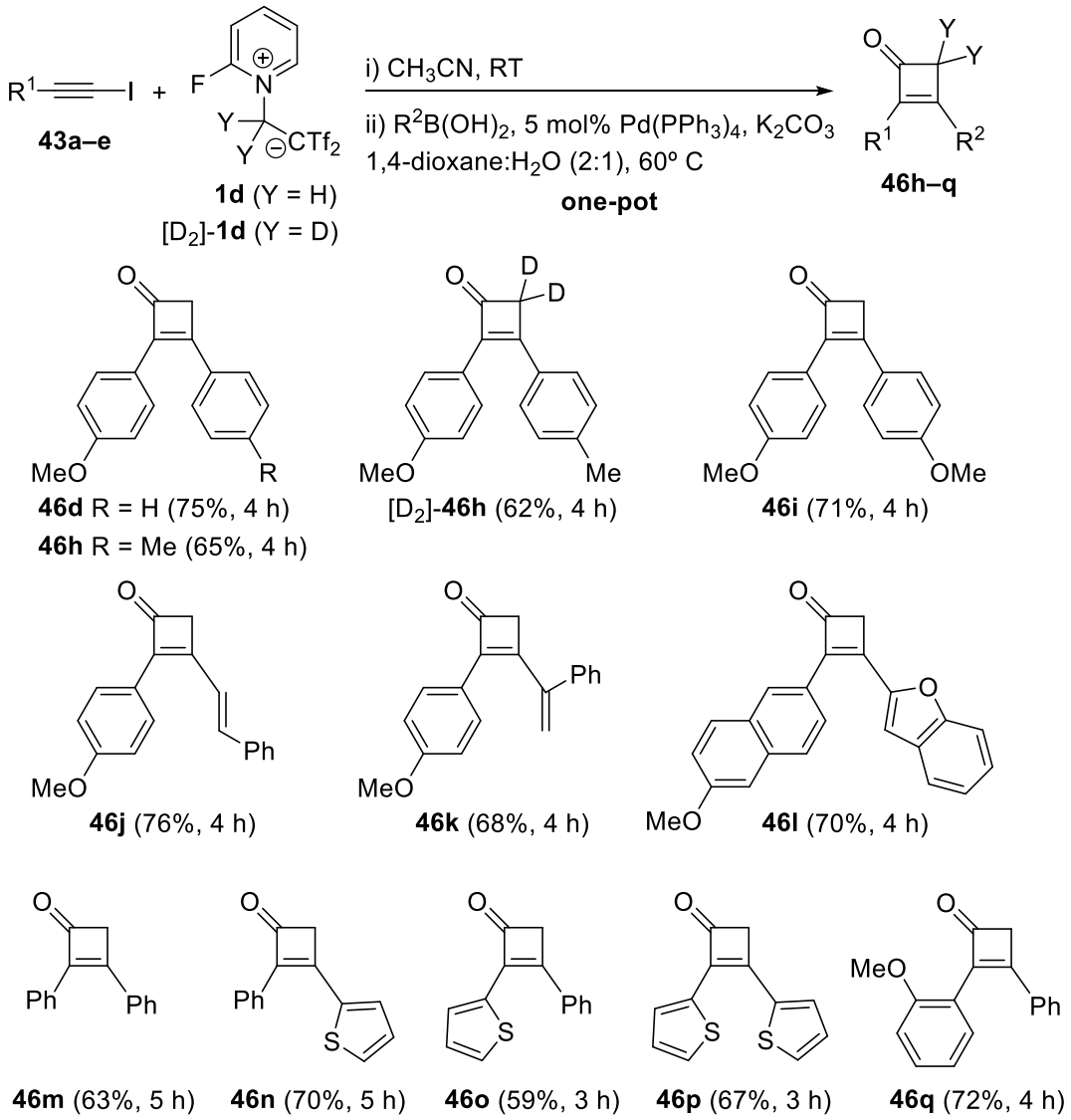
Scheme VII.3. Palladium-catalyzed reaction of bis(triflyl)iodocyclobutenes **44a–c** with stannanes. Regiocontrolled synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones **46d–g**.

A one-pot iodocyclobutene formation and C–C coupling process would be more convenient, but the one-pot alkyne activation/cross-coupling/ketone formation reactions present several reactivity challenges. Thus, treatment of iodoalkynes **43** with Yanai's reagent **1d** in acetonitrile at RT was followed by solvent removal. The unpurified bis(triflyl)iodocyclobutenes **44** were combined with the appropriate cross-coupling reagent following the standard procedures. Interestingly, Heck and Stille conditions were amenable for the one-pot protocol starting from iodoalkyne **43a**

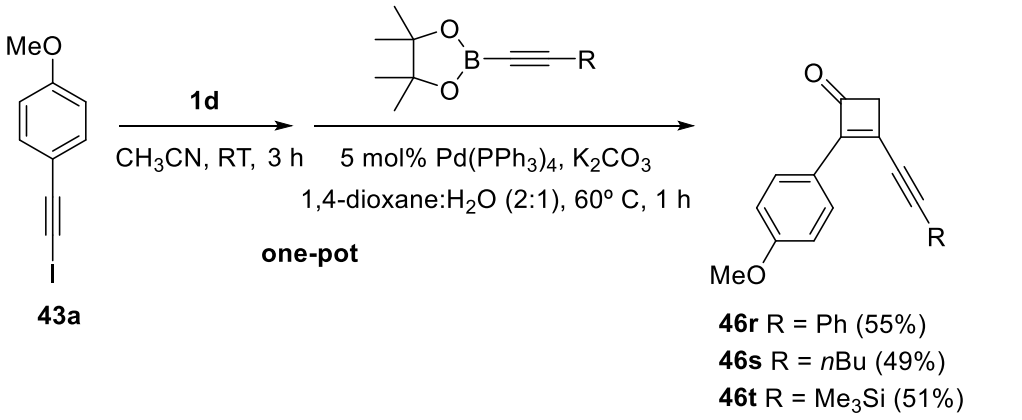
(Scheme VII.4). Taking into account the high purity of crude bis(triflyl)iodocyclobutenes **44**, we believe that Suzuki conditions would be even more satisfactory for operating under one-pot procedure.[7] Consequently, we used Suzuki conditions in the cross-coupling of in situ generated bis(triflyl)iodocyclobutenes **44** through the utilization of a one-pot procedure. Delightfully, starting from the appropriate iodoalkyne **43** and Yanai's reagent **1d**, followed by the addition of the corresponding boronic acid and the palladium catalyst, the one-pot protocol can be efficiently accomplished. In this way, differently functionalized 2,3-disubstituted-cyclobut-2-en-1-ones **46** were directly obtained in good yields from iodoalkynes **43** without laborious isolation of any intermediates (Scheme VII.5 and Scheme VII.6), which in terms of simplicity and effectiveness is more appealing. This simple and versatile one-pot procedure is successfully applied to the convenient preparation of 2,3-diaryl-cyclobut-2-en-1-ones, 2-aryl-3-alkenyl-cyclobut-2-en-1-ones, and 2-aryl-3-alkynyl-cyclobut-2-en-1-ones. In the last case, alkynylboronic acid pinacol esters were used as the cross-coupling partners (Scheme VII.6). Gratifyingly, a salient feature of the present method is the facile access to deuterated compounds such as 2-(4-methoxyphenyl)-3-(4-tolyl)cyclobut-2-en-1-one-4,4-d_2 [D_2]-**5h** (Scheme VII.5).[8]



Scheme VII.4. One-pot preparation of 2,3-disubstituted-cyclobut-2-en-1-ones **46a,d**.

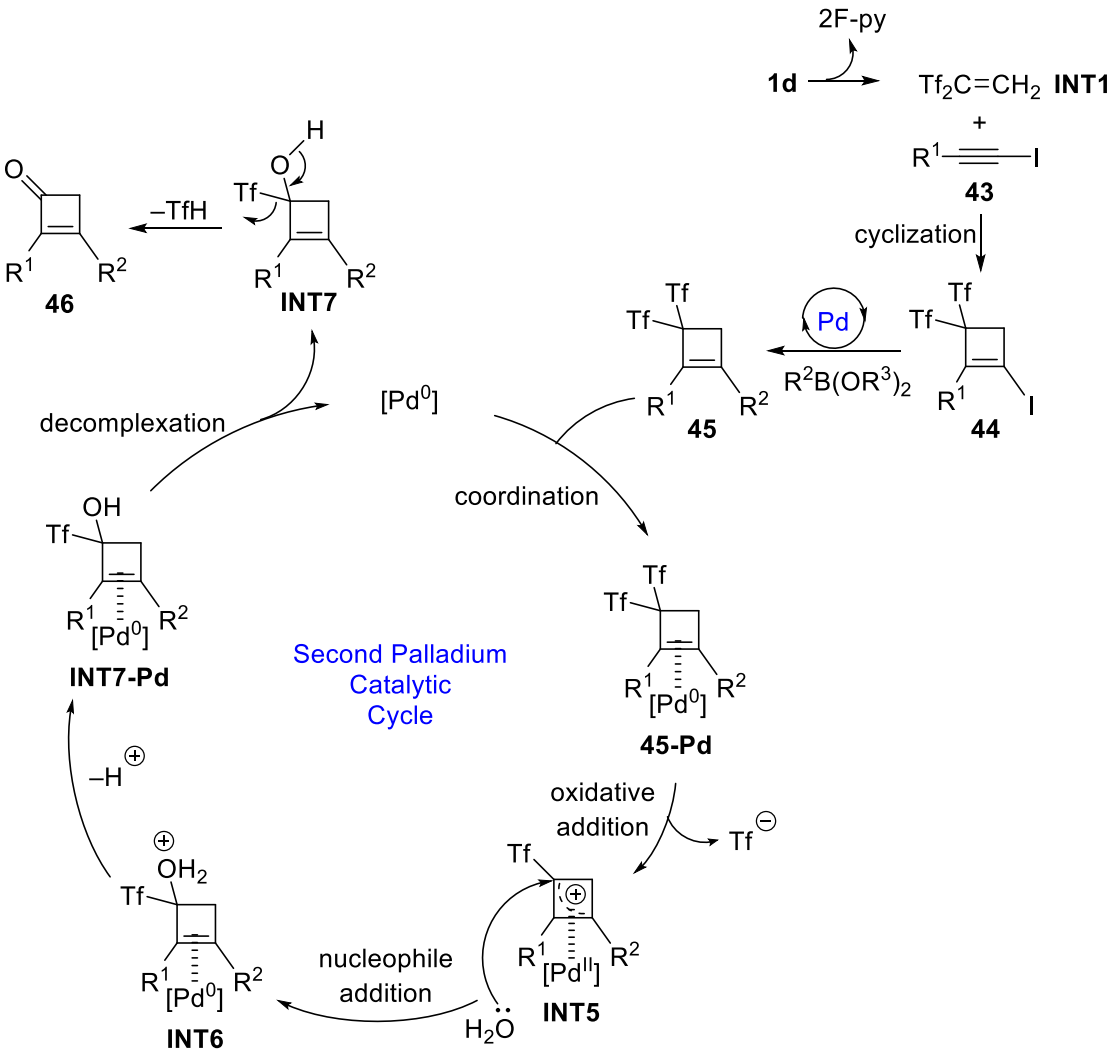


Scheme VII.5. One-pot controlled preparation of 2,3-diaryl-cyclobut-2-en-1-ones **46h**,**i**, [D_2]-**46h**, **46l–q** and 2-aryl-3-alkenyl-cyclobut-2-en-1-ones **46j**,**k**.



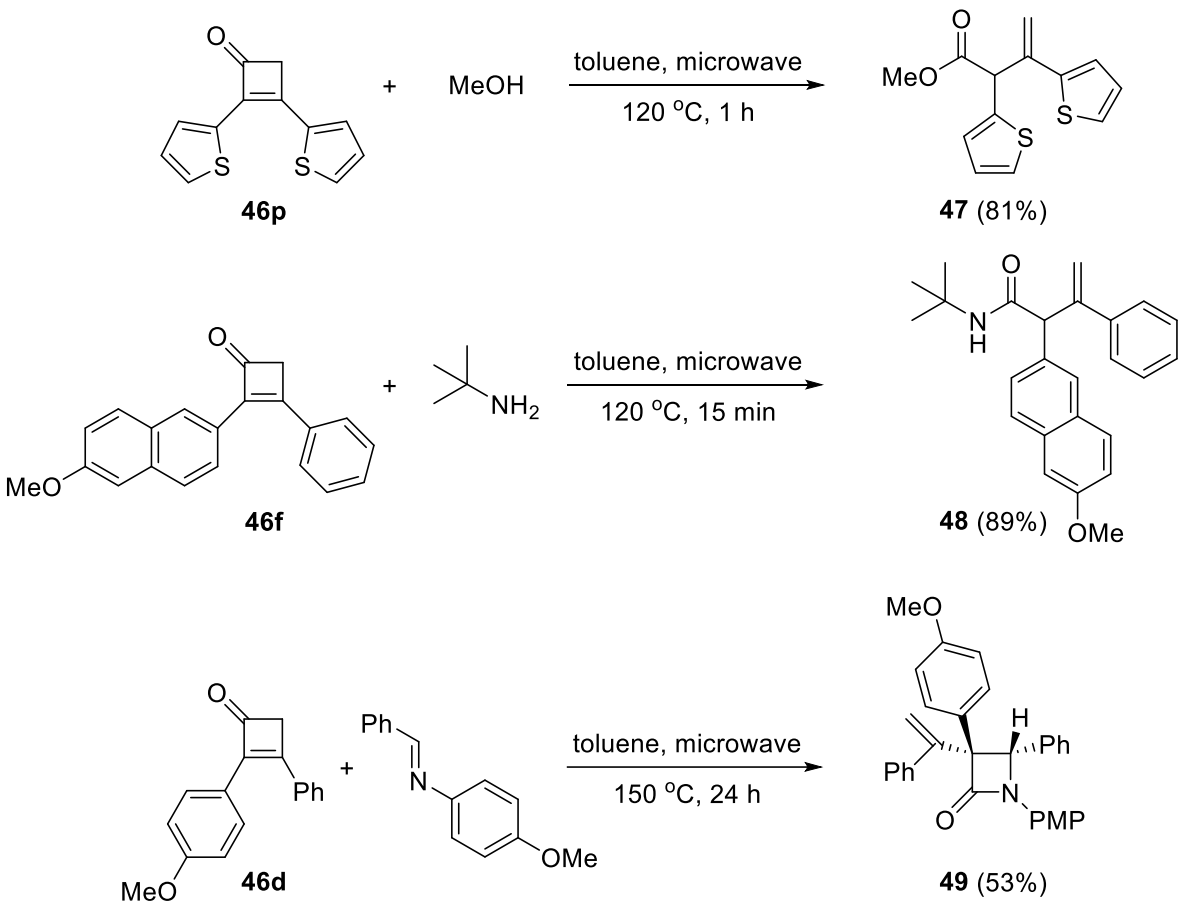
Scheme VII.6. One-pot controlled preparation of 2-aryl-3-alkynyl-cyclobut-2-en-1-ones **46r–t**.

In Scheme VII.7 we propose a reaction mechanism for our one-pot sequence. Initially, iodoalkynes **43** are converted into bis(triflyl)iodocyclobutenes **44** by cyclization reaction with the *in situ* generated 1,1-bis[(trifluoromethyl)sulfonyl]ethene **INT1**. Adducts **44** further react with boronic acids or boronic acid pinacol esters under Pd-catalyzed conditions to complete the first palladium catalytic cycle wit concurrent formation of intermediate bis(triflyl)cyclobutenes **45**. The $Pd(PPh_3)_4$ also facilitates the formation of Tf-cyclobutenol intermediates **INT7** through an allylic substitution reaction (second catalytic cycle). After coordination, the Pd^0 species should promote oxidative addition with the allyl substrates **45** which bear a leaving group (Tf) by generation of π-allyl palladium species **INT5**. These formed Pd^{II} species are very reactive and suffer a selective nucleophilic attack by water at the 1-position to form intermediates **INT6**, which after proton release and decomplexation should liberate Tf-cyclobutenols **INT7** with concomitant regeneration of the palladium catalytic species. Final TfH loss gives rise to the observed 2,3-disubstituted-cyclobut-2-en-1-ones **46**.



Scheme VII.7. Proposed reaction pathway for the one-pot preparation of 2,3-disubstituted-cyclobut-2-en-1-ones **46** from iodoalkynes **43** under Suzuki conditions.

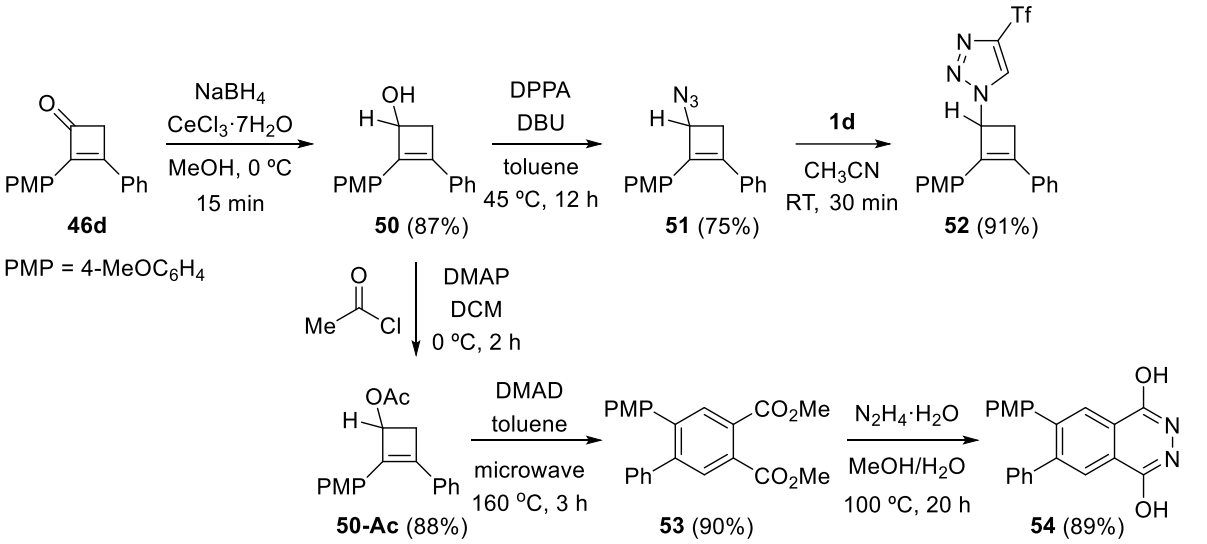
Taking into account the inherent ring strain associated to the cyclobutenone ring, we next focused on the transformation of the above prepared 2,3-disubstituted-cyclobut-2-en-1-ones **46**. In the event, thermal ring opening and subsequent trap of the resulting ketene was attained in the presence of several reagents such as methanol, *tert*-butylamine and *N*-(4-methoxyphenyl)-1-phenylmethanimine (Scheme VII.8). Worthy of note, the β-lactam **49**[9] was obtained in a totally stereoselective fashion through transannulation of cyclobutenone **46d** (Scheme VII.8).



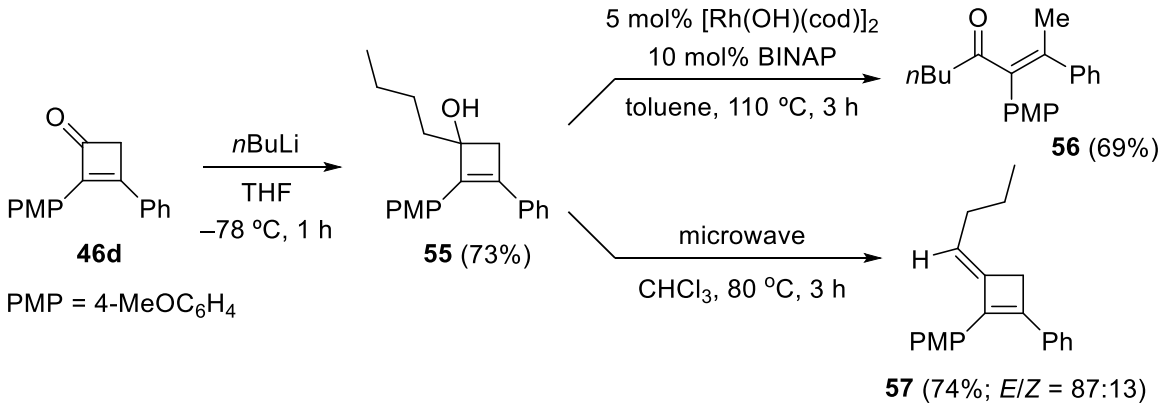
Scheme VII.8. Ring opening or transannulation reactions of cyclobutenones **46**. Controlled preparation of 2,3-disubstituted-but-3-enoate **47**, 2,3-disubstituted-but-3-enamide **48** and β-lactam **49**.

As an additional application of the prepared carbocycles **46**, the reduction of cyclobut-2-en-1-one **46d** to cyclobutenol **50** and its further synthetic utility were attempted (Scheme VII.9). Cyclobutenyl-triazole **52** and the tetrasubstituted benzene **53** were obtained in good overall yields. The convenient preparation of cyclobutenyl-triazole **52** was accomplished from cyclobutenol **50** through sequential treatment with diphenyl phosphoryl azide (DPPA) and Yanai's reagent **1d**.[10] The ring-expanded product **53** was formed very well from acetate **50-Ac** *via* the thermal cascade reaction between an *in situ* formed diene and dimethylacetylene dicarboxylate (DMAD). The dimethyl phthalate derivative **53** was treated with hydrazine hydrate and converted into the 6,7-disubstituted-phthalazine-1,4-diol **54**.[11] We also explored the addition of organometallic reagents to the cyclobutenone core and associated ring transformations. A 73% yield of quaternary cyclobutenol **55** was obtained after the reaction of cyclobutenone **46d** with *n*BuLi (Scheme VII.10). The α,β-unsaturated

ketone **56** arising from a rhodium-catalyzed ring-opening reaction of **55** was achieved as single *Z*-isomer. A dehydration occurred by refluxing **55** in chloroform to afford the cyclobutadiene **57** (Scheme VII.10).



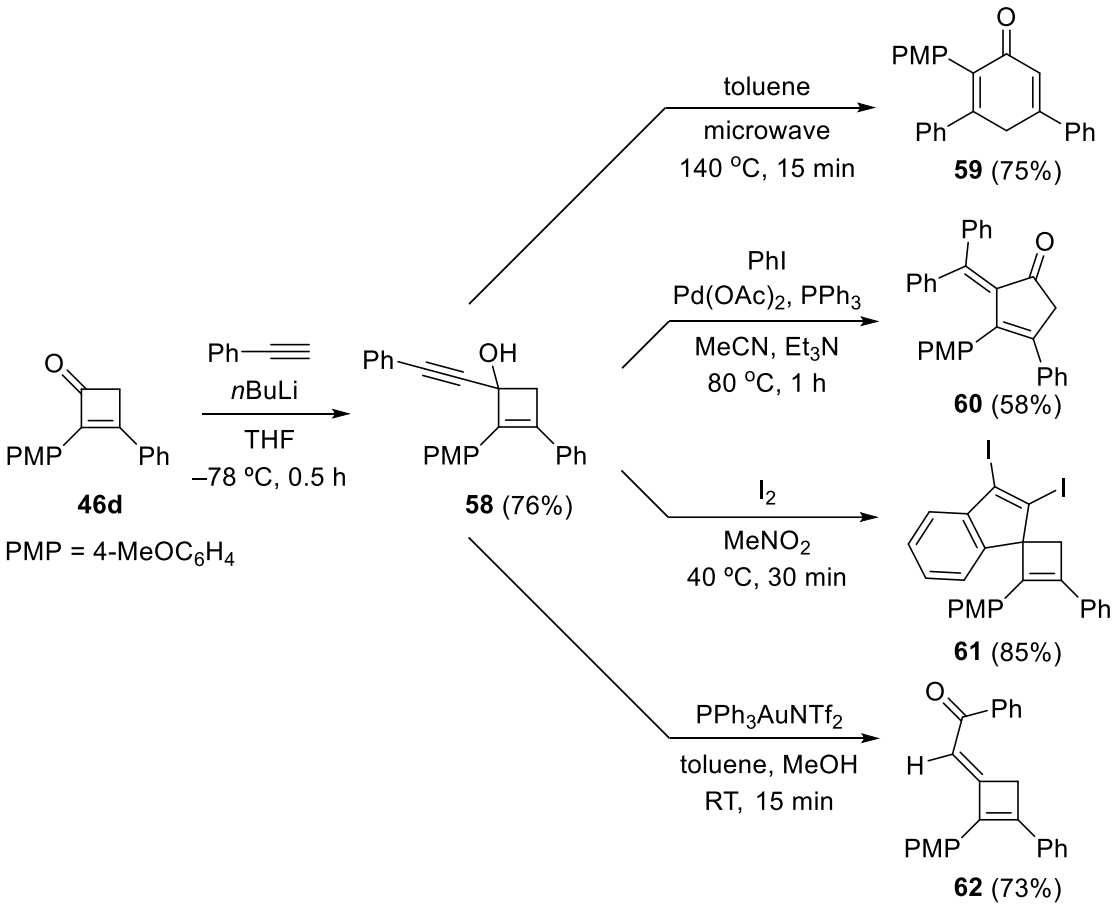
Scheme VII.9. Reduction and ring expansion reactions of cyclobutenone **46d**. Controlled preparation of cyclobutenyl-triazole **52** and phthalazine derivative **54**.



Scheme VII.10. Alkenylation and ring opening reactions of cyclobutenone **46d**. Controlled preparation of α,β-unsaturated ketone **56** and cyclobutadiene **57**.

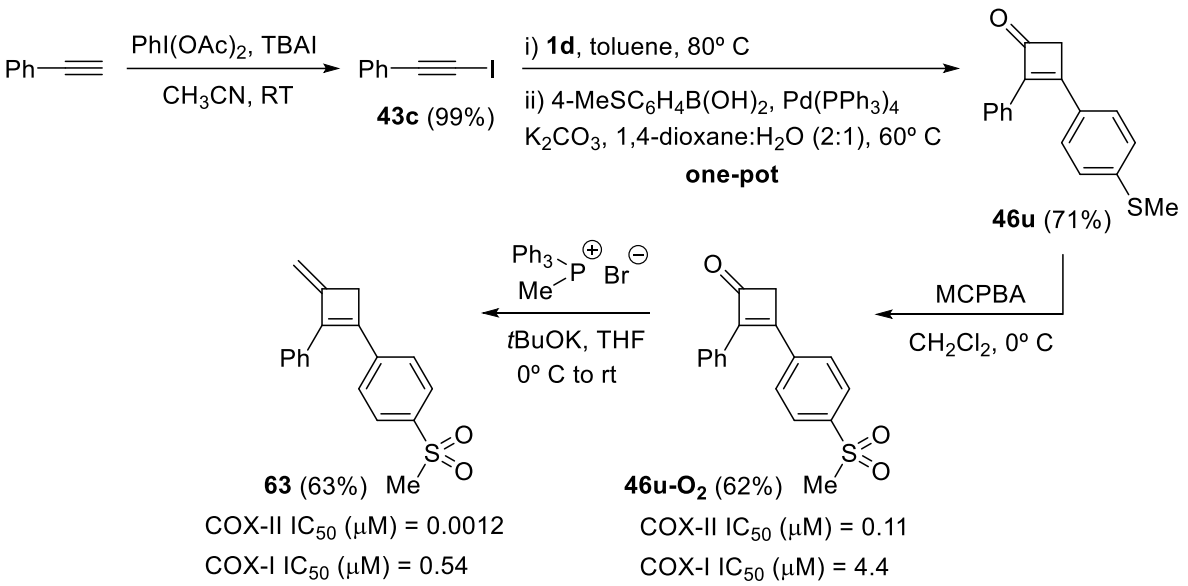
Next, we proposed cyclobutene-tethered alkynol **58**, which was readily prepared from cyclobut-2-en-1-one **46d** through the reaction with lithium phenylacetylide, as a platform for the achievement of different structural motifs (Scheme VII.11). Interestingly, the thermal two-carbon ring enlargement was easily accomplished to form trisubstituted cyclohexa-2,5-dien-1-one **59**. Also, the synthesis of trisubstituted cyclopent-3-en-1-one **60** based on a Pd-catalyzed C–C coupling–

one-atom ring expansion cascade was consummated. Besides, spirocyclic cyclobutene **61** and the Meyer–Schuster rearranged adduct **62** were smoothly synthesized.



Scheme VII.11. Alkenylation, spirocyclization and ring expansion reactions of cyclobutenone **46d**. Controlled preparation of cyclohexa-2,5-dien-1-one **59**, cyclopent-3-en-1-one **60**, spirocyclic cyclobutene **61**, and cyclobutadienone **62**.

The efficiency of this novel cyclobutenone construction method, paved the way for the preparation of bioactive products bearing related structural motifs. As a proof of concept, we directed our efforts towards the synthesis of cyclobutadiene **63**, an orally active cyclooxygenase (COX) II inhibitor [COX-II IC_{50} (μM) = 0.0012; COX-I IC_{50} (μM) = 0.54], which has been previously prepared from phenylacetylene in an overall 1.7% yield.[12] Our proposal was based on the straightforward synthesis of 2,3-disubstituted-cyclobut-2-en-1-one **46u** followed by selective *S*-oxidation and alkenylation reactions. In this way, the synthesis of compound **63** was reached from phenylacetylene in an overall 27% yield (Scheme VII.12).



Scheme VII.12. Efficient preparation of the selective cyclooxygenase (COX) inhibitor **63**.

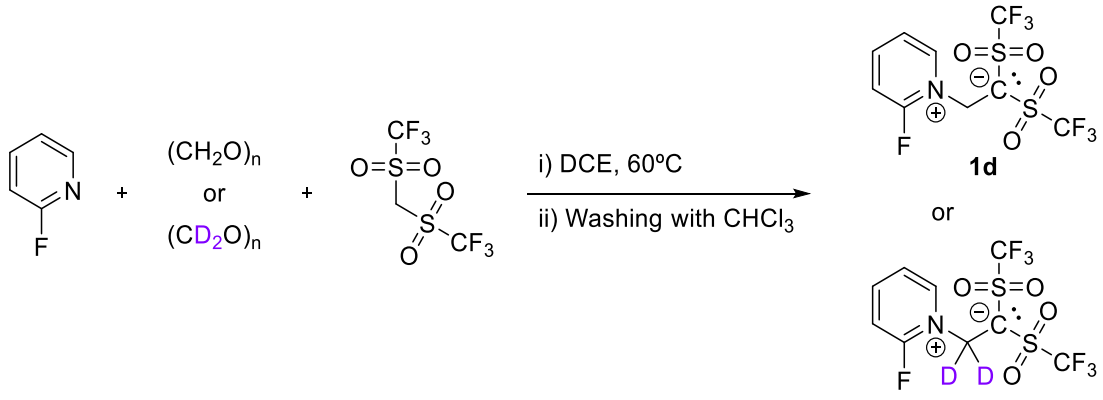
VII.2.3. Conclusion

In summary, we have developed a regioselective one-pot synthesis of cyclobutenones from yodoalkynes through sequential bis(triflyl)cyclobutenylation and Suzuki reaction with concomitant ketone formation. This one-pot methodology has been used for the efficient synthesis of a selective an orally active cyclooxygenase II inhibitor. Besides, the obtained 2,3-disubstituted-cyclobut-2-en-1-ones were used as useful synthons in several transformations such as for the preparation of 2,3-disubstituted-but-3-enoates, β-lactams, phthalazines, α,β-unsaturated ketones, cyclobutadienes, cyclohexa-2,5-dien-1-ones, and cyclopent-3-en-1-ones.

VII.3. Experimental Section

General Methods: ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance AMX-700, Bruker AMX-500, or Bruker Avance-DPX 300. NMR spectra were recorded in $CDCl_3$, C_6D_6, CD_3CN, or DMSO-d_6 solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm), or DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Chemical shifts in ^{19}F are given in ppm relative to (trifluoromethyl)benzene ($C_6H_5CF_3$) in $CDCl_3$ (^{19}F, –63.7 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification. Microwave irradiation was carried out in a Monowave 300 from Anton Paar GmbH. The reaction temperatures during microwave heating were measured with an internal infrared sensor.

Yanai's reagent **1d** was synthesized according to a literature procedure: H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi, T. Matsumoto, *Chem. Commun.* **2013**, *49*, 10091. Novel deuterated azolium salt [D_2]-**1d** was prepared adapting the same procedure.



To a solution of Tf_2CH_2 (281 mg, 1.00 mmol) in 1,2-dichloroethane (6.0 mL), paraformaldehyde (90% purity, 73.0 mg, 2.19 mmol) or paraformaldehyde-d_2 (98% purity, 98 atom % D, 64 mg, 2.00 mmol) and 2-fluoropyridine (172 µL, 2.00 mmol) were added at room temperature. After being stirred for 8 h at 60 °C, the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with $CHCl_3$ (1.0 mLx3) to give zwitterion **1d** in 91% yield (356 mg, 0.915 mmol) or [D_2]-**1d** in 86% yield (336 mg, 0.858 mmol).

Deuterated Yanais'reagent [D_2]-**1d.** From 281 mg (1.0 mmol) of CH_2Tf_2, 336 mg (86%) of compound [D_2]-**1d** was obtained as a colorless solid; mp 161–163 ºC; ^{1}H NMR (700 MHz, CD_3CN, 25 ºC): δ = 8.99 (s, 1H, CH^{Ar}), 8.64 (m, 1H, CH^{Ar}), 7.95 (m, 1H, CH^{Ar}), 7.78 (m, 1, CH^{Ar}); ^{13}C NMR (175 MHz, CD_3CN, 25 ºC): δ = 158.7 (d, J_{CF} = 278.8 Hz, $C^{Ar\text{-}q}$-F), 151.1 (d, J_{CF} = 9.9 Hz, CH^{Ar}), 142.0 (CH^{Ar}), 124.4 (CH^{Ar}), 120.7 (q, J_{CF} = 325.4 Hz, $2CF_3$), 114.3 (d, J_{CF} = 21.3 Hz, CH^{Ar}), 67.1 (CTf_2-*broad*), 56.6 (CD_2- *broad*); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –79.6 (s, 1F, F), –80.5 (s, 6F, $2CF_3$); D(^{2}H) NMR (107 MHz, CD_3CN, 25 ºC): δ = 5.63 (s, 2D, CD_2); IR (KBr): ν = 1345, 1101 (O=S=O), 1192 (C–F) cm^{-1}.

General procedure for the palladium-catalyzed Heck reaction/ketone formation of bis(triflyl)iodocyclobutenes 44. Synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones 46a–c. A solution of the appropriate bis(triflyl)iodocyclobutene **44** (1.0 mmol), the

corresponding alkene (3.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol, 5.0 mol %), and triethylamine (3.0 mmol) in acetonitrile (10 mL) was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3x15 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **46a–c** follow.

Methyl (*E*)-3-(2-(4-methoxyphenyl)-3-oxocyclobut-1-en-1-yl)acrylate 46a. From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **44a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5 → 9:1) as eluent gave compound **46a** (11 mg, 47%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 8.00 (d, 1H, *J* = 15.3 Hz, C*H*=CH), 7.72 (m, 2H, $2CH^{Ar}$), 6.61 (m, 2H, $2CH^{Ar}$), 5.80 (d, 1H, *J* = 15.3 Hz, CH=C*H*), 3.43 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 2.86 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 188.0 (C=O), 166.0 (C=OO), 161.1 ($C^{Ar\text{-}q}$-OCH_3), 151.9 (*C*=C), 147.5 (C=*C*), 134.1 (H*C*=CH), 129.9 ($2CH^{Ar}$), 128.0 (HC=*C*H), 122.9 ($C^{Ar\text{-}q}$), 114.7 ($2CH^{Ar}$), 54.7 (OCH_3), 51.5 (OCH_3), 48.9 (CH_2); IR (CH_2Cl_2): ν = 1744 (C=O), 1726 (C=OO) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}O_4$ [*M* + H]$^+$: 259.09649; found: 259.09772.

(*E*)-3-(2-(4-Methoxyphenyl)-3-oxocyclobut-1-en-1-yl)acrylonitrile 46b. From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **44a**, and after flash chromatography of the residue using hexanes/toluene (1:1) as eluent gave compound **46b** (10 mg, 51%) as a yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.48 (m, 2H, $2CH^{Ar}$), 6.94 (d, 1H, *J* = 15.8 Hz, C*H*=CH), 6.67 (m, 2H, $2CH^{Ar}$), 4.35 (d, 1H, *J* = 15.8 Hz, CH=C*H*), 3.22 (s, 3H, OCH_3), 2.62 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 187.3 (C=O), 161.5 ($C^{Ar\text{-}q}$-OCH_3), 150.1 (*C*=C), 147.1 (C=*C*), 138.9 (H*C*=CH), 122.3 ($C^{Ar\text{-}q}$), 117.1 (CN), 114.8 ($2CH^{Ar}$), 106.0 (HC=*C*H), 54.8 (OCH_3), 48.5 (CH_2); IR (CH_2Cl_2): ν = 1742 (C=O), 2221 (CN) cm^{-1}.

(*E*)-2-(6-Methoxynaphthalen-2-yl)-3-styrylcyclobut-2-en-1-one 46c. From 65 mg (0.11 mmol) of bis(triflyl)iodocyclobutene **44b**, and after flash chromatography of the residue using hexanes/diethyl ether (9:1) as eluent gave compound **46c** (22 mg, 63%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.27 (s, 1H, CH^{Ar}), 7.80 (m, 4H, $3CH^{Ar}$, C*H*=CH), 7.65 (m, 2H, $2CH^{Ar}$), 7.45 (m, 3H, $3CH^{Ar}$), 7.17 (m, 2H, $2CH^{Ar}$), 7.04 (d, 1H, *J* = 15.5 Hz, CH=C*H*), 3.95 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 189.0 (C=O), 158.5 ($C^{Ar\text{-}q}$-OCH_3), 158.4 (*C*=C), 143.1 (H*C*=CH), 141.5 (C=*C*), 135.6 ($C^{Ar\text{-}q}$), 134.4 ($C^{Ar\text{-}q}$), 130.1 ($2CH^{Ar}$), 129.1 ($2CH^{Ar}$), 128.8 ($C^{Ar\text{-}q}$), 128.0 ($2CH^{Ar}$), 127.3 (CH^{Ar}), 127.2 (CH^{Ar}), 125.7 ($C^{Ar\text{-}q}$), 125.0 (CH^{Ar}), 120.3 (HC=*C*H), 119.4 (CH^{Ar}), 105.9 (CH^{Ar}), 55.3 (OCH_3), 48.9 (CH_2); IR ($CHCl_3$): ν = 1738 (C=O), 1593 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{19}O_2$ [*M* + H]$^+$: 327.13796; found: 327.13839.

General procedure for the palladium-catalyzed Stille reaction/ketone formation of bis(triflyl)iodocyclobutenes 44. Synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 46d–g. A solution of the appropriate bis(triflyl)iodocyclobutene **44** (1.0 mmol), the corresponding stannane (5.0 mmol), and $Pd(PPh_3)_2Cl_2$ (0.05 mmol, 5.0 mol %) in *N*,*N*-dimethylformamide (10 mL) was heated in a sealed tube at 70 °C until disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3x15 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **46d–g** follow.

2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-one 46d. From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **44a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **46d** (18 mg, 80%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.77 (m, 2H, 2CH^{Ar}), 7.68 (m, 2H, 2CH^{Ar}), 7.48 (m, 3H, 3CH^{Ar}), 6.95 (m, 2H, 2CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.62 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 188.4 (C=O), 159.9 (*C*=C), 159.8 (*C*$^{Ar\text{-}q}$-OCH_3), 141.3 (*C*$^{Ar\text{-}q}$), 132.7 (C=*C*), 131.2 (CH^{Ar}), 129.1 (2CH^{Ar}), 128.8 (2CH^{Ar}), 128.7 (2CH^{Ar}), 122.3 (C$^{Ar\text{-}q}$), 114.1 (2CH^{Ar}), 55.3 (OCH_3), 49.5 (CH_2); IR ($CHCl_3$): ν = 1739 (C=O), 1607 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}O_2$ [*M* + H]$^+$: 251.10666; found: 251.10776.

2-(4-Methoxyphenyl)-3-vinylcyclobut-2-en-1-one 46e. From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **44a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **46e** (8 mg, 45%) as a yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ^{o}C): δ = 7.75 (m, 2H, 2CH^{Ar}), 6.82 (dd, 1H, *J* = 16.9, 10.2 Hz, C*H*=CH_2), 6.74 (m, 2H, 2CH^{Ar}), 5.24 (dd, 1H, *J* = 10.2, 1.4 Hz, CH=C*H*H), 5.05 (dd, 1H, *J* = 16.9, 1.4 Hz, CH=CH*H*), 3.22 (s, 3H, OCH_3), 2.98 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ^{o}C): δ = 187.7 (C=O), 160.4 (*C*$^{Ar\text{-}q}$-OCH_3), 156.4 (*C*=C), 142.3 (C=*C*), 129.4 (2CH^{Ar}), 129.3 (H*C*=CH_2), 126.5 (HC=*C*H_2), 123.7 (C$^{Ar\text{-}q}$), 114.5 (2CH^{Ar}), 54.7 (OCH_3), 48.5 (CH_2); IR ($CHCl_3$): ν = 1743 (C=O) cm^{-1}.

2-(6-Methoxynaphthalen-2-yl)-3-phenylcyclobut-2-en-1-one 46f. From 28 mg (0.05 mmol) of bis(triflyl)iodocyclobutene **44b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **46f** (10 mg, 72%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 8.18 (s, 1H, CH^{Ar}), 7.77 (m, 5H, 5CH^{Ar}), 7.48 (m, 3H, 3CH^{Ar}), 7.17 (m, 2H, 2CH^{Ar}), 3.95 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 188.3 (C=O), 161.1 (*C*$^{Ar\text{-}q}$-OMe), 158.5 (*C*=C), 141.8 (C=*C*), 134.6 (C$^{Ar\text{-}q}$), 132.7 (C$^{Ar\text{-}q}$), 131.5 (CH^{Ar}), 130.0 (CH^{Ar}), 128.9 (2CH^{Ar}), 128.8 (2CH^{Ar}), 128.7 (C$^{Ar\text{-}q}$), 127.4 (CH^{Ar}), 123.1 (CH^{Ar}), 125.2 (CH^{Ar}), 124.9 (C$^{Ar\text{-}q}$), 119.3 (CH^{Ar}), 105.8 (CH^{Ar}), 55.3 (OCH_3), 49.7 (CH_2); IR ($CHCl_3$): ν = 1737 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{17}O_2$ [*M* + H]$^+$: 301.12231; found: 301.12241.

2-Phenyl-3-(phenylethynyl)cyclobut-2-en-1-one 46g. From 30 mg (0.06 mmol) of bis(triflyl)iodocyclobutene **44c**, and after flash chromatography of the residue using hexanes/diethyl ether (95:5) as eluent gave compound **46g** (9 mg, 65%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 8.02 (m, 2H, 2CH^{Ar}), 7.62 (m, 2H, 2CH^{Ar}), 7.43 (m, 6H, 6CH^{Ar}), 3.61 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 189.3 (C=O), 148.8 (*C*=C), 141.0 (C=*C*), 132.0 (2CH^{Ar}), 130.3 (CH^{Ar}), 129.7 (C$^{Ar\text{-}q}$), 129.6 (CH^{Ar}), 128.7 (2CH^{Ar}), 128.6 (2CH^{Ar}), 126.9 (2CH^{Ar}), 121.7 (C$^{Ar\text{-}q}$), 114.0 (*C*≡C), 83.9 (C≡*C*), 52.7 (CH_2); IR ($CHCl_3$): ν = 1719 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{13}O$ [*M* + H]$^+$: 245.09609; found: 245.09571.

General procedure for the one-pot synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones 46 using Heck reaction conditions. Yanais'reagent **1d** (0.1 mmol) was added at room temperature to a solution of the appropriate alkyne **43** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC). The corresponding alkene (0.3 mmol), $Pd(PPh_3)_4$ (0.005 mmol, 5.0 mol %), and triethylamine (0.3 mmol) in acetonitrile (0.5 mL) were added to the above crude bis(triflyl)cyclobutene **44**. The resulting solution was heated in a sealed tube at 80 ^{o}C until disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3x5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds.

General procedure for the one-pot synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 46 using Stille reaction conditions. Yanais'reagent **1d** (0.1 mmol) was added at room temperature to a solution of the appropriate alkyne **43** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC). After removal of the acetonitrile, the corresponding stannane (0.5 mmol), and $Pd(PPh_3)_2Cl_2$ (0.005 mmol, 5.0 mol %) in *N*,*N*-dimethylformamide (2 mL) were added to the above crude bis(triflyl)cyclobutene **44**. The resulting solution was heated in a sealed tube at 70 °C until disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3x5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds.

General procedure for the one-pot synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 46h–u and [D_2]-46h using Suzuki reaction conditions. Yanais'reagent **1d** or deuterated Yanais'reagent [D_2]-**1d** (0.1 mmol) was added at room temperature to a solution of the appropriate alkyne **43** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC). After removal of the acetonitrile, the corresponding boronic acid or boronic ester (0.15 mmol), K_2CO_3 (0.3 mmol) and 1,4-dioxane/water (2:1) (1.5 mL) were added to the above crude bis(triflyl)cyclobutene **3**. The reaction was stirred at rt for 10 min. Then, $Pd(PPh_3)_4$ (0.005 mmol, 5.0 mol %) was added and the resulting mixture was heated in a sealed tube at 60 °C until disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3x5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **5h–u** and [D_2]-**5h** follow.

2-(4-Methoxyphenyl)-3-(*p*-tolyl)cyclobut-2-en-1-one 46h. From 80 mg (0.14 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3 → 9:1) as eluent gave compound **46h** (24 mg, 65%) as a colorless solid; mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.67 (m, 4H, 4CH^{Ar}), 7.27 (m, 2H, 2CH^{Ar}), 6.94 (m, 2H, 2CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 188.5 (C=O), 160.0 (C=*C*), 159.8 (*C*$^{Ar\text{-}q}$-OCH_3), 142.1 (*C*$^{Ar\text{-}q}$), 140.4 (*C*=C), 130.0 (C$^{Ar\text{-}q}$), 129.5 (2CH^{Ar}), 129.0 (2CH^{Ar}), 128.8 (2CH^{Ar}), 122.5 (C$^{Ar\text{-}q}$), 114.0 (2CH^{Ar}), 55.3 (OCH_3), 49.4 (CH_2), 21.7 (CH_3); IR ($CHCl_3$): ν = 1741 (C=O), 1607 (C=C), 1249 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{17}O_2$ [*M* + H]$^+$: 265.12231; found: 265.12146.

2-(4-Methoxyphenyl)-3-(*p*-tolyl)cyclobut-2-en-1-one-4,4-*d*$_2$ [D_2]-46h. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound [D_2]-**46h** (15 mg, 62%) as a colorless solid; mp 103–105 °C; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): δ = 7.67 (m, 4H, 4CH^{Ar}), 7.27 (m, 2H, 2CH^{Ar}), 6.94 (m, 2H, 2CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): δ = 188.5 (C=O), 159.9 (C=*C*), 159.8 (*C*$^{Ar\text{-}q}$-OCH_3), 142.1 (*C*$^{Ar\text{-}q}$), 140.6 (*C*=C), 130.0 (C$^{Ar\text{-}q}$), 129.5 (2CH^{Ar}), 129.0 (2CH^{Ar}), 128.9 (2CH^{Ar}), 122.5 (C$^{Ar\text{-}q}$), 114.0 (2CH^{Ar}), 55.3 (OCH_3), 48.8 (m, CD_2), 21.7 (CH_3); D(^{2}H) NMR (107 MHz, $CDCl_3$, 25 °C): δ = 3.56 (s, 2D, CD_2); IR ($CHCl_3$): ν = 1740 (C=O), 1608 (C=C), 1247 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{14}D_2NaO_2$ [*M* + Na]$^+$: 289.11680; found: 289.11641.

2,3-Bis(4-methoxyphenyl)cyclobut-2-en-1-one 46i. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **46i** (18 mg, 71%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$,

25 ºC): δ = 7.73 (m, 2H, 2CH^{Ar}), 7.65 (m, 2H, 2CH^{Ar}), 6.96 (m, 4H, 4CH^{Ar}), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 188.1 (C=O), 162.1 (C=*C*), 159.9 (*C*$^{Ar\text{-}q}$-OCH_3), 159.7 (*C*$^{Ar\text{-}q}$-OCH_3), 139.2 (*C*=C), 130.9 (2CH^{Ar}), 129.0 (2CH^{Ar}), 125.5 (C$^{Ar\text{-}q}$), 122.7 (C$^{Ar\text{-}q}$), 114.3 (2CH^{Ar}), 114.1 (2CH^{Ar}), 55.5 (OCH_3), 55.3 (OCH_3), 49.3 (CH_2); IR ($CHCl_3$): ν = 1744 (C=O), 1601 (C=C), 1256 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{17}O_3$ [*M* + H]$^+$: 281.11720; found: 281.11690.

(*E*)-2-(4-Methoxyphenyl)-3-styrylcyclobut-2-en-1-one 46j. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/diethyl ether (95:5 → 9:1) as eluent gave compound **46j** (19 mg, 76%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.75 (m, 2H, 2CH^{Ar}), 7.67 (d, 1H, *J* = 15.6 Hz, C*H*=CH), 7.61 (m, 2H, 2CH^{Ar}), 7.43 (m, 3H, 3CH^{Ar}), 6.97 (m, 3H, C*H*=CH, 2CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 188.9 (C=O), 159.8 (*C*$^{Ar\text{-}q}$-OCH_3), 157.0 (*C*=C), 142.6 (H*C*=CH), 141.1 (C=*C*), 135.5 (C$^{Ar\text{-}q}$), 129.9 (CH^{Ar}), 129.0 (2CH^{Ar}), 128.9 (2CH^{Ar}), 127.9 (2CH^{Ar}), 123.7 (C$^{Ar\text{-}q}$), 120.2 (HC=*C*H), 114.2 (2CH^{Ar}), 55.3 (OCH_3), 48.6 (CH_2); IR ($CHCl_3$): ν = 1738 (C=O), 1593 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{17}O_2$ [*M* + H]$^+$: 277.12231; found: 277.12102.

2-(4-Methoxyphenyl)-3-(1-phenylvinyl)cyclobut-2-en-1-one 46k. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **46k** (17 mg, 68%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.30 (m, 5H, 5CH^{Ar}), 7.02 (m, 2H, 2CH^{Ar}), 7.6.59 (m, 2H, 2CH^{Ar}), 5.93 (d, 1H, *J* = 1.0 Hz, =C*H*H), 5.77 (d, 1H, *J* = 1.0 Hz, =CH*H*), 3.74 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 189.6 (C=O), 159.5 (*C*$^{Ar\text{-}q}$-OCH_3), 157.6 (*C*=C), 144.2 (*C*=CH_2), 142.4 (C=*C*), 137.8 (C$^{Ar\text{-}q}$), 130.1 (2CH^{Ar}), 128.5 (2CH^{Ar}), 128.3 (CH^{Ar}), 127.8 (2CH^{Ar}), 125.2 (C=*C*H_2), 121. (C$^{Ar\text{-}q}$), 113.1 (2CH^{Ar}), 55.1 (OCH_3), 50.6 (CH_2); IR ($CHCl_3$): ν = 1722 (C=O), 1615 (C=C) cm^{-1}.

3-(Benzofuran-2-yl)-2-(6-methoxynaphthalen-2-yl)cyclobut-2-en-1-one 46l. From 30 mg (0.05 mmol) of iodoalkyne **43b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **46l** (12 mg, 70%) as a colorless solid; mp 165–167 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.68 (s, 1H, CH^{Ar}), 7.74 (dd, 1H, *J* = 8.5, 1.6 Hz, CH^{Ar}), 7.84 (m, 2H, 2CH^{Ar}), 7.69 (m, 2H, 2CH^{Ar}), 7.49 (m, 1H, CH^{Ar}), 7.35 (m, 1H, CH^{Ar}), 7.18 (m, 3H, 3CH^{Ar}), 3.96 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 188.2 (C=O), 158.6 (*C*$^{Ar\text{-}q}$-OMe), 156.7 (C=*C*), 150.2 (C$^{Ar\text{-}q}$), 144.2 (C$^{Ar\text{-}q}$), 140.9 (*C*=C), 134.8 (C$^{Ar\text{-}q}$), 130.4 (CH^{Ar}), 128.6 (C$^{Ar\text{-}q}$), 128.4 (CH^{Ar}), 127.9 (C$^{Ar\text{-}q}$), 127.5 (CH^{Ar}), 127.0 (CH^{Ar}), 125.8 (CH^{Ar}), 124.9 (C$^{Ar\text{-}q}$), 123.9 (CH^{Ar}), 122.4 (CH^{Ar}), 119.2 (CH^{Ar}), 114.3 (CH^{Ar}), 111.9 (CH^{Ar}), 105.8 (CH^{Ar}), 55.3 (OCH_3), 49.2 (CH_2); IR ($CHCl_3$): ν = 1739 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{17}O_3$ [*M* + H]$^+$: 341.11722; found: 341.11729.

2,3-Diphenylcyclobut-2-en-1-one 46m. From 30 mg (0.06 mmol) of iodoalkyne **43c**, and after flash chromatography of the residue using hexanes/diethyl ether (97:3) as eluent gave compound **46m** (8 mg, 63%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.78 (m, 2H, 2CH^{Ar}), 7.71 (m, 2H, 2CH^{Ar}), 7.44 (m, 6H, 6CH^{Ar}), 3.66 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 188.0 (C=O), 162.7 (C=*C*), 141.7 (*C*=C), 132.4 (C$^{Ar\text{-}q}$), 131.6 (CH^{Ar}), 129.7 (C$^{Ar\text{-}q}$), 129.0 (2CH^{Ar}), 128.9 (2CH^{Ar}), 128.7 (2CH^{Ar}), 127.6 (2CH^{Ar}), 49.6 (CH_2); IR ($CHCl_3$): ν = 1739 (C=O), 1610 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{13}O$ [*M* + H]$^+$: 221.09609; found: 221.09634.

2-Phenyl-3-(thiophen-2-yl)cyclobut-2-en-1-one 46n. From 30 mg (0.06 mmol) of iodoalkyne **43c**, and after flash chromatography of the residue using hexanes/diethyl ether (98:2) as eluent gave compound **46n** (9 mg, 70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.85 (m, 2H, 2CH^{Ar}), 7.70 (dd, 1H, *J* = 5.0, 1.0 Hz, CH^{Ar}), 7.55 (dd, 1H, *J* = 3.7,

1.0 Hz, CH^{Ar}), 7.42 (m, 3H, $3CH^{Ar}$), 7.24 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 3.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 187.4 (C=O), 153.0 (C=*C*), 139.0 (*C*=C), 135.5 ($C^{Ar\text{-}q}$), 133.1 (CH^{Ar}), 132.6 (CH^{Ar}), 129.5 ($C^{Ar\text{-}q}$), 128.9 (CH^{Ar}), 128.7 ($2CH^{Ar}$), 128.4 (CH^{Ar}), 127.5 ($2CH^{Ar}$), 50.7 (CH_2); IR ($CHCl_3$): ν = 1743 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}OS$ [*M* + H]$^+$: 227.05251; found: 227.05309.

3-Phenyl-2-(thiophen-2-yl)cyclobut-2-en-1-one 46o. From 30 mg (0.06 mmol) of iodoalkyne **43d**, and after flash chromatography of the residue using hexanes/diethyl ether (97:3) as eluent gave compound **46o** (8 mg, 59%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.92 (m, 2H, $2CH^{Ar}$), 7.74 (d, 1H, *J* = 3.5 Hz, CH^{Ar}), 7.54 (m, 3H, $3CH^{Ar}$), 7.41 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 7.14 (dd, 1H, *J* = 5.0, 3.7 Hz, CH^{Ar}), 3.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 186.8 (C=O), 157.6 (C=*C*), 132.4 (*C*=C), 131.5 (CH^{Ar}), 130.3 ($C^{Ar\text{-}q}$), 129.1 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 128.9 (CH^{Ar}), 127.5 (CH^{Ar}), 126.6 (CH^{Ar}), 49.9 (CH_2); IR ($CHCl_3$): ν = 1745 (C=O), 1602 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{11}OS$ [*M* + H]$^+$: 227.05251; found: 227.05261.

2,3-Di(thiophen-2-yl)cyclobut-2-en-1-one 46p. From 50 mg (0.09 mmol) of iodoalkyne **43d**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **46p** (15 mg, 67%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.80 (d, 1H, *J* = 3.5 Hz, CH^{Ar}), 7.77 (dd, 1H, *J* = 5.0, 1.1 Hz, CH^{Ar}), 7.62 (dd, 1H, *J* = 3.7, 1.0 Hz, CH^{Ar}), 7.44 (dd, 1H, *J* = 5.0, 0.9 Hz, CH^{Ar}), 7.28 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 7.16 (dd, 1H, *J* = 5.0, 3.7 Hz, CH^{Ar}), 3.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 185.9 (C=O), 148.3 (C=*C*), 135.5 (*C*=C), 132.9 ($2CH^{Ar}$), 132.3 ($C^{Ar\text{-}q}$), 130.2 ($C^{Ar\text{-}q}$), 128.6 (CH^{Ar}), 128.4 (CH^{Ar}), 127.5 (CH^{Ar}), 126.7 (CH^{Ar}), 51.1 (CH_2); IR ($CHCl_3$): ν = 1741 (C=O), 1590 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{12}H_9OS_2$ [*M* + H]$^+$: 233.00893; found: 233.00953.

2-(2-Methoxyphenyl)-3-phenylcyclobut-2-en-1-one 46q. From 52 mg (0.094 mmol) of iodoalkyne **43e**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **46q** (17 mg, 72%) as a colorless solid; mp 101–103 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.53 (m, 3H, $3CH^{Ar}$), 7.41 (m, 4H, $4CH^{Ar}$), 7.01 (m, 2H, $2CH^{Ar}$), 3.72 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 188.1 (C=O), 163.1 (*C*=C), 156.9 ($C^{Ar\text{-}q}$-OCH_3), 139.1 ($C^{Ar\text{-}q}$), 132.8 (C=*C*), 131.1 (CH^{Ar}), 130.1 (CH^{Ar}), 129.8 ($2CH^{Ar}$), 128.2 ($2CH^{Ar}$), 120.6 (CH^{Ar}), 119.0 ($C^{Ar\text{-}q}$), 111.1 (CH^{Ar}), 55.1 (OCH_3), 49.2 (CH_2); IR ($CHCl_3$): ν = 1735 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{14}NaO_2$ [*M* + Na]$^+$: 273.08860; found: 273.08872.

2-(4-Methoxyphenyl)-3-(phenylethynyl)cyclobut-2-en-1-one 46r. From 33 mg (0.06 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **46r** (9 mg, 55%) as a yellow solid; mp 134–136 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.98 (m, 2H, $2CH^{Ar}$), 7.61 (m, 2H, $2CH^{Ar}$), 7.45 (m, 3H, $3CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 3.86 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 189.7 (C=O), 160.5 ($C^{Ar\text{-}q}$-OCH_3), 148.5 (*C*=C), 138.0 (C=*C*), 131.9 ($2CH^{Ar}$), 130.0 (CH^{Ar}), 128.7 ($2CH^{Ar}$), 128.5 ($2CH^{Ar}$), 122.7 ($C^{Ar\text{-}q}$), 121.9 ($C^{Ar\text{-}q}$), 114.1 ($2CH^{Ar}$), 113.0 (*C*≡C), 84.1 (C≡*C*), 55.3 (OCH_3), 52.5 (CH_2); IR ($CHCl_3$): ν = 2198 (C≡C), 1726 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{15}O_2$ [*M* + H]$^+$: 275.10666; found: 275.10790.

3-(Hex-1-yn-1-yl)-2-(4-methoxyphenyl)cyclobut-2-en-1-one 46s. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/toluene (3:7) as eluent gave compound **46s** (9 mg, 55%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.90 (m, 2H, $2CH^{Ar}$), 6.91 (m, 2H, $2CH^{Ar}$), 3.84 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2), 2.65 (t, 2H, *J* = 7.0 Hz, CH_2), 1.61 (m, 4H, $2CH_2$), 0.99 (t, 3H, *J* = 7.3 Hz,

CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 190.2 (C=O), 160.2 ($C^{Ar\text{-}q}$-OCH_3), 147.7 (*C*=C), 140.1 (C=*C*), 128.2 ($2CH^{Ar}$), 122.7 ($C^{Ar\text{-}q}$), 116.9 (*C*≡C), 113.9 ($2CH^{Ar}$), 76.2 (C≡*C*), 55.3 (OCH_3), 52.5 (CH_2), 30.3 (CH_2), 22.0 (CH_2), 20.4 (CH_2), 13.6 (CH_3); IR ($CHCl_3$): ν = 2202 (C≡C), 1719 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{19}O_2$ [*M* + H]$^+$: 255.13796; found: 255.13771.

2-(4-Methoxyphenyl)-3-((trimethylsilyl)ethynyl)cyclobut-2-en-1-one 46t. From 50 mg (0.09 mmol) of iodoalkyne **43a**, and after flash chromatography of the residue using hexanes/ethyl acetate (98:2) as eluent gave compound **46t** (12 mg, 51%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.92 (m, 2H, $2CH^{Ar}$), 6.92 (m, 2H, $2CH^{Ar}$), 3.85 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2), 0.33 (s, 9H, $3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 190.1 (C=O), 160.6 ($C^{Ar\text{-}q}$-OCH_3), 149.5 (*C*=C), 137.7 (C=*C*), 128.5 ($2CH^{Ar}$), 122.5 ($C^{Ar\text{-}q}$), 121.1 (*C*≡C), 114.0 ($2CH^{Ar}$), 98.6 (C≡*C*), 55.3 (OCH_3), 52.5 (CH_2), –0.45 ($3CH_3$); IR ($CHCl_3$): ν = 1723 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{19}O_2Si$ [*M* + H]$^+$: 271.11488; found: 271.11611.

3-(4-(Methylthio)phenyl)-2-phenylcyclobut-2-en-1-one 46u. From 50 mg (0.1 mmol) of iodoalkyne **43c**, and after flash chromatography of the residue using hexanes/diethyl ether (9:1 → 85:15) as eluent gave compound **46u** (19 mg, 71%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.59 (m, 2H, $2CH^{Ar}$), 7.31 (m, 3H, $3CH^{Ar}$), 7.20 (m, 2H, $2CH^{Ar}$), 3.53 (s, 2H, CH_2), 2.46 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 187.8 (C=O), 161.1 (*C*=C), 144.3 ($C^{Ar\text{-}q}$), 140.8 ($C^{Ar\text{-}q}$), 129.9 (C=*C*), 129.3 ($2CH^{Ar}$), 128.8 (CH^{Ar}), 128.7 ($2CH^{Ar}$), 128.6 ($C^{Ar\text{-}q}$), 127.6 ($2CH^{Ar}$), 125.4 ($2CH^{Ar}$), 49.4 (CH_2), 14.8 (SCH_3); IR ($CHCl_3$): ν = 1739 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{14}NaOS$ [*M* + Na]$^+$: 289.06576; found: 289.06602.

General procedure for the ring opening or transannulation reactions of cyclobutenones 46. **Synthesis of 2,3-disubstituted-but-3-enoate 47, 2,3-disubstituted-but-3-enamide 48 and β-lactam 49**. A stirred solution of the corresponding cyclobutenone **46** (0.05 mmol) and the appropriate reagent [methanol, *tert*-butylamine or *N*-(4-methoxyphenyl)-1-phenylmethanimine] in toluene (1.0 mL) was heated at the adequate temperature under microwave irradiation until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes or diethyl ether/hexanes mixtures. Spectroscopic and analytical data for pure forms of compounds **47**–**49** follow.

Methyl 2,3-di(thiophen-2-yl)but-3-enoate 47. From 13 mg (0.09 mmol) of cyclobutenone **46p**, and after flash chromatography of the residue using hexanes/diethyl ether (97:3) as eluent gave compound **47** (12 mg, 81%) as a colorless oil; ^1H NMR (500 MHz, C_6D_6, 25 °C): δ = 6.96 (m, 2H, $2CH^{Ar}$), 6.81 (dd, 1H, *J* = 5.2, 1.1 Hz, CH^{Ar}), 6.67 (m, 2H, $2CH^{Ar}$), 6.58 (dd, 1H, *J* = 5.1, 3.7 Hz, CH^{Ar}), 5.64 (s, 1H, CH), 5.27 (s, 1H, =C*H*H), 5.16 (s, 1H, =CH*H*), 3.23 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 171.0 (C=O), 143.8 (*C*=CH_2), 139.8 ($C^{Ar\text{-}q}$), 139.3 ($C^{Ar\text{-}q}$), 127.6 (CH^{Ar}), 127.3 (CH^{Ar}), 126.8 (CH^{Ar}), 125.7 (CH^{Ar}), 124.9 (CH^{Ar}), 124.6 (CH^{Ar}), 114.9 (C=*C*H_2), 52.0 (OCH_3), 51.9 (CH); IR (CH_2Cl_2): ν = 1739 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}O_2S_2$ [*M* + H]$^+$: 265.03515; found: 265.03407.

***N*-(*tert*-Butyl)-2-(6-methoxynaphthalen-2-yl)-3-phenylbut-3-enamide 48.** From 10 mg (0.03 mmol) of cyclobutenone **46f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **48** (11 mg, 89%) as a colorless solid; mp 154–156 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.71 (m, 3H, $3CH^{Ar}$), 7.43 (m, 3H, $3CH^{Ar}$), 7.30 (m, 3H, $3CH^{Ar}$), 7.43 (m, 2H, $2CH^{Ar}$), 5.71 (s, 1H, CH), 5.62 (NH), 5.16 (s, 1H, =C*H*H), 4.88 (s, 1H, =CH*H*), 3.92 (s, 3H, OCH_3), 1.30 (s, 9H, $3CH_3$); ^{13}C NMR (75 MHz,

$CDCl_3$, 25 °C): δ = 170.8 (C=O), 158.2 ($C^{Ar\text{-}q}$-OCH_3), 147.9 (*C*=CH_2), 141.3 ($C^{Ar\text{-}q}$), 134.2 ($C^{Ar\text{-}q}$), 133.8 ($C^{Ar\text{-}q}$), 129.8 (CH^{Ar}), 129.4 ($C^{Ar\text{-}q}$), 128.8 ($2CH^{Ar}$), 128.2 (CH^{Ar}), 128.0 (CH^{Ar}), 127.8 (CH^{Ar}), 127.7 (CH^{Ar}), 119.3 (CH^{Ar}), 117.2 (C=*C*H_2), 106.0 (CH^{Ar}), 60.0 (CH), 55.7 (OCH_3), 51.8 (C^{Cq}-N), 28.9 ($3CH_3$); IR ($CHCl_3$): ν = 1638 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{28}NO_2$ [*M* + H]$^+$: 374.21146; found: 374.21121.

(3*RS*,4*SR*)-1,3-Bis(4-methoxyphenyl)-4-phenyl-3-(1-phenylvinyl)azetidin-2-one 49. From 13 mg (0.05 mmol) of cyclobutenone **46d**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **49** (13 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.60 (m, 2H, $2CH^{Ar}$), 7.28 (m, 2H, $2CH^{Ar}$), 7.13 (m, 2H, $2CH^{Ar}$), 6.97 (m, 3H, $3CH^{Ar}$), 6.80 (m, 4H, $4CH^{Ar}$), 6.33 (m, 2H, $2CH^{Ar}$), 6.01 (d, 1H, *J* = 0.9 Hz, =C*H*H), 5.61 (s, 1H, CH), 5.44 (d, 1H, *J* = 0.9 Hz, =CH*H*), 3.84 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.6 (C=O), 159.1 ($C^{Ar\text{-}q}$-OCH_3), 156.0 ($C^{Ar\text{-}q}$-OCH_3), 144.3 (*C*=C), 139.3 ($C^{Ar\text{-}q}$), 134.6 ($C^{Ar\text{-}q}$), 130.8 ($C^{Ar\text{-}q}$), 130.4 ($C^{Ar\text{-}q}$), 128.6 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 128.0 (CH^{Ar}), 127.9 ($2CH^{Ar}$), 127.4 ($2CH^{Ar}$), 127.1 ($2CH^{Ar}$), 126.6 (CH^{Ar}), 119.1 (=CH_2), 118.8 ($2CH^{Ar}$), 114.2 ($2CH^{Ar}$), 114.1 ($2CH^{Ar}$), 72.4 (C^{Cq}), 65.4 (CH), 55.4 (OCH_3), 55.3 (OCH_3); IR ($CHCl_3$): ν = 1746 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{31}H_{28}NO_3$ [*M* + H]$^+$: 462.20637; found: 462.20539.

Procedure for the ketone reduction reaction of cyclobutenone 46d. **Synthesis of cyclobutenol 50**. $NaBH_4$ (0.098 mmol) was added portionwise to a cooled solution (0 °C) of $CeCl_3 \cdot 7H_2O$ (0.105 mmol) and cyclobutenone **46d** (0.07 mmol, 17 mg) in MeOH (0.3 mL). Next, the reaction mixture was warmed up to room temperature and stirred for 1 hour. The reaction mixture was filtrated by a short pad of celite and the solvent was removed by vacuum. After then, water was added and the mixture was extracted with AcOEt (3x5 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (8:2) to give cyclobutenol **50** (12 mg, 87%) as a colorless oil.

2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-ol 50. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.57 (m, 4H, $4CH^{Ar}$), 7.34 (m, 3H, $3CH^{Ar}$), 6.91 (m, 2H, $2CH^{Ar}$), 5.02 (dd, 1H, 4.1, 1.0 Hz, CH), 3.84 (s, 3H, OCH_3), 3.10 (dd, 1H, *J* = 13.0, 4.2 Hz, C*H*H), 2.69 (dd, 1H, *J* = 13.0, 0.8 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 159.3 ($C^{Ar\text{-}q}$-OCH_3), 140.9 (*C*=C), 136.1 ($C^{Ar\text{-}q}$), 135.0 ($C^{Ar\text{-}q}$), 128.4 ($2CH^{Ar}$), 128.2 (CH^{Ar}), 128.1 ($2CH^{Ar}$), 126.6 ($2CH^{Ar}$), 126.1 (C=*C*), 114.0 ($2CH^{Ar}$), 67.1 (CH), 55.3 (OCH_3), 39.7 (CH_2); IR ($CHCl_3$): ν = 3487 (OH) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{17}O_2$ [*M* + H]$^+$: 253.12231; found: 253.12143.

Procedure for the esterification reaction of cyclobutenol 50. **Synthesis of cyclobutenyl acetate 50-Ac**. Acetyl chloride (0.18 mmol), Et_3N (0.44 mmol), and DMAP (cat.) were added to a cooled solution (0 °C) of cyclobutenol **50** (0.15 mmol) in dichloromethane (5 mL). Next, the reaction mixture was stirred for 2 hours. After then, water was added and the mixture was extracted with dichloromethane (3x5 mL). The combined organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (95:5) to give acetate **50-Ac** (38 mg, 88%) as a colorless oil.

2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-yl acetate 50-Ac. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.53 (m, 4H, $4CH^{Ar}$), 7.35 (m, 3H, $3CH^{Ar}$), 6.90 (m, 2H, $2CH^{Ar}$), 5.92 (dd, 1H, 4.1, 1.1 Hz, CH), 3.84 (s, 3H, OCH_3), 3.18 (dd, 1H, *J* = 13.2, 4.2 Hz, C*H*H), 2.82

(dd, 1H, *J* = 13.2, 1.0 Hz, CH*H*), 2.09 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 171.2 (C=O), 159.4 ($C^{Ar\text{-}q}$-OCH_3), 137.4 (*C*=C), 137.2 ($C^{Ar\text{-}q}$), 134.5 ($C^{Ar\text{-}q}$), 128.5 (CH^{Ar}), 128.4 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 126.6 ($2CH^{Ar}$), 125.8 (C=*C*), 113.9 ($2CH^{Ar}$), 67.7 (CH), 55.2 (OCH_3), 36.9 (CH_2), 21.2 (CH_3); IR ($CHCl_3$): ν = 1738 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}NaO_3$ [*M* + Na]$^+$: 317.11482; found: 317.11471.

Procedure for the azidation reaction of cyclobutenol 50. **Synthesis of cyclobutenyl-azide 51**. Diphenyl phosphoryl azide (0.14 mmol) and DBU (0.14 mmol) were added to a solution of cyclobutenol **50** (23 mg, 0.11 mmol) in toluene (8 mL). Next, the reaction mixture was warmed at 45 ºC overnight. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with hexanes/ethyl acetate (97:3) to give azide **51** (23 mg, 75%) as a colorless oil.

1-(4-Azido-2-phenylcyclobut-1-en-1-yl)-4-methoxybenzene 51. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.55 (m, 4H, $4CH^{Ar}$), 7.35 (m, 3H, $3CH^{Ar}$), 6.92 (m, 2H, $2CH^{Ar}$), 4.54 (d, 1H, 3.0 Hz, CH), 3.85 (s, 3H, OCH_3), 3.11 (dd, 1H, *J* = 13.2, 4.4 Hz, C*H*H), 2.92 (dd, 1H, *J* = 13.2, 1.4 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.6 ($C^{Ar\text{-}q}$-OCH_3), 137.4 (*C*=C), 137.2 ($C^{Ar\text{-}q}$), 134.4 ($C^{Ar\text{-}q}$), 128.6 (CH^{Ar}), 128.5 ($2CH^{Ar}$), 128.0 ($2CH^{Ar}$), 126.6 ($2CH^{Ar}$), 125.9 (C=*C*), 114.1 ($2CH^{Ar}$), 55.8 (CH), 55.3 (OCH_3), 35.0 (CH_2); IR ($CHCl_3$): ν = 2125 (N=N=N) cm^{-1}.

Procedure for the triazole formation reaction of cyclobutenyl-azide 51. **Synthesis of cyclobutenyl-triazole 52**. Zwitterion **1d** (1.0 mmol) was added at room temperature to a solution of the azide-cyclobutene **51** (1.0 mmol) in acetonitrile (8.0 mL). Next, the reaction mixture was stirred for 30 min until disappearance of the starting material by TLC. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (9:1) to give triazole-cyclobutene **52** (33 mg, 91%) as a colorless solid.

1-(2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-yl)-4-((trifluoromethyl)sulfonyl)-1*H*-1,2,3-triazole 52. Mp 144–146 ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.25 (s, 1H, CH^{Ar}-*triazole*), 7.61 (m, 2H, $2CH^{Ar}$), 7.39 (m, 5H, $5CH^{Ar}$), 6.88 (m, 2H, $2CH^{Ar}$), 6.14 (dd, 1H, 4.6, 1.6 Hz, CH), 3.83 (s, 3H, OCH_3), 3.53 (dd, 1H, *J* = 13.7, 4.7 Hz, C*H*H), 3.08 (dd, 1H, *J* = 13.7, 1.6 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.3 ($C^{Ar\text{-}q}$-OCH_3), 139.4 (*C*=C), 139.3 ($C^{Ar\text{-}q}$), 134.5 ($C^{Ar\text{-}q}$), 133.2 ($C^{Ar\text{-}q}$), 129.7 (CH^{Ar}), 129.9 (CH^{Ar}), 128.8 ($2CH^{Ar}$), 127.8 ($2CH^{Ar}$), 126.5 ($2CH^{Ar}$), 123.7 (C=*C*), 119.4 (q, J_{CF} = 324.8 Hz, CF_3), 114.7 ($2CH^{Ar}$), 56.1 (CH), 55.4 (OCH_3), 38.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.3 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1368, 1085 (O=S=O), 1206 (C–F); HRMS (ES): calcd for $C_{20}H_{16}F_3N_3NaO_3S$ [*M* + Na]$^+$: 453.07752; found: 458.07567.

Procedure for the ring opening/Diels–Alder reaction of cyclobutenyl acetate 50-Ac. **Synthesis of phthalate 53**. A stirred solution of cyclobutenyl acetate **50-Ac** (30 mg, 0.10 mmol) and dimethylacetylene dicarboxylate (0.50 mmol) in toluene (1.0 mL) was heated at at 160 °C under microwave irradiation for 3 h. The reaction was allowed to cool to room temperature. Then, the solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (95:5→9:1) to give phthalate **53** (34 mg, 90%) as a colorless oil.

Dimethyl 4-methoxy-[1,1':2',1''-terphenyl]-4',5'-dicarboxylate 53. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.81 (s, 1H, CH^{Ar}), 7.79 (s, 1H, CH^{Ar}), 7.27 (m, 3H, $3CH^{Ar}$), 7.17 (m,

2H, 2CH^{Ar}), 7.08 (m, 2H, 2CH^{Ar}), 6.79 (m, 2H, 2CH^{Ar}), 3.97 (s, 3H, $COOCH_3$), 3.96 (s, 3H, $COOCH_3$), 3.81 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 168.0 (C=O), 167.8 (C=O), 159.0 (*C*$^{Ar\text{-}q}$-OCH_3), 143.1 (*C*$^{Ar\text{-}q}$), 143.1 (*C*$^{Ar\text{-}q}$), 131.8 (*C*$^{Ar\text{-}q}$), 131.4 (CH^{Ar}), 131.0 (CH^{Ar}), 130.9 (*C*$^{Ar\text{-}q}$), 130.8 (2CH^{Ar}), 130.1 (*C*$^{Ar\text{-}q}$), 129.6 (2CH^{Ar}), 128.2 (2CH^{Ar}), 127.3 (CH^{Ar}), 113.6 (2CH^{Ar}), 55.2 (OCH_3), 52.7 (CH_3), 52.6 (CH_3); IR ($CHCl_3$): ν = 1741 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{21}O_5$ [*M* + H]$^+$: 377.13835; found: 377.13788.

Procedure for the heterocyclization reaction of phthalate 53. **Synthesis of phthalazine 54**. Hydrazine monohydrate (2.4 mol) was added to a solution of phthalate **53** (10 mg, 0.002 mol) in a mixture methanol:water (1:1, 10 mL). Next, the reaction mixture was heated at 100 °C for 20 h. The reaction was allowed to cool to room temperature. Then, the white solid was filtered and rinsed with water and methanol to give phthalazine **54** (8 mg, 89%) as a colorless solid.

6-(4-Methoxyphenyl)-7-phenylphthalazine-1,4-diol 54. Mp 290–292 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, 25 ºC): δ = 7.99 (s, 1H, CH^{Ar}), 7.98 (s, 1H, CH^{Ar}), 7.32 (m, 3H, 3CH^{Ar}), 7.20 (m, 2H, 2CH^{Ar}), 7.11 (m, 2H, 2CH^{Ar}), 6.85 (m, 2H, 2CH^{Ar}), 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 158.6 (*C*$^{Ar\text{-}q}$-OCH_3), 154.9 (*C*$^{Ar\text{-}q}$), 143.9 (*C*$^{Ar\text{-}q}$), 143.7 (*C*$^{Ar\text{-}q}$), 139.9 (*C*$^{Ar\text{-}q}$), 131.8 (*C*$^{Ar\text{-}q}$), 130.7 (2CH^{Ar}), 129.3 (2CH^{Ar}), 128.3 (2CH^{Ar}), 127.4 (CH^{Ar}), 127.0 (CH^{Ar}), 126.7 (CH^{Ar}), 126.6 (*C*$^{Ar\text{-}q}$), 126.3 (*C*$^{Ar\text{-}q}$), 113.7 (2CH^{Ar}), 55.0 (OCH_3); HRMS (ES): calcd for $C_{21}H_{16}N_2NaO_3$ [*M* + Na]$^+$: 367.10531; found: 367.10513.

Procedure for the addition reaction of *n*-butyllithium to cyclobutenone 46d. **Synthesis of cyclobutenol 55**. A cooled solution of *n*-BuLi (0.14 mmol) in hexanes (0.09 mL) was added dropwise to a stirred solution of cyclobutenone **46d** (30 mg, 0.12 mmol) in THF (0.4 mL) at –78 °C. After 1 h, saturated ammonium chloride (0.5 mL) was added and the reaction mixture was allowed to warm to rt. Then, the mixture was extracted with ethyl acetate (3x5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave cyclobutenol **55** (27 mg, 73%) as a colorless oil.

1-Butyl-2-(4-methoxyphenyl)-3-phenylcyclobut-2-en-1-ol 55. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.58 (m, 2H, 2CH^{Ar}), 7.52 (m, 2H, 2CH^{Ar}), 7.32 (m, 3H, 3CH^{Ar}), 6.89 (m, 2H, 2CH^{Ar}), 3.84 (s, 3H, OCH_3), 3.00 (d, 1H, *J* = 12.8 Hz, C*H*H), 2.66 (d, 1H, *J* = 12.8 Hz, CH*H*), 2.01 (m, 2H, OH, C*H*H), 1.81 (m, 1H, CH*H*), 1.39 (m, 4H, $2CH_2$), 3.00 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.1 (*C*$^{Ar\text{-}q}$-OCH_3), 142.5 (*C*=C), 136.4 (*C*$^{Ar\text{-}q}$), 135.2 (*C*$^{Ar\text{-}q}$), 128.3 (4CH^{Ar}), 128.0 (CH^{Ar}), 126.5 (2CH^{Ar}), 113.8 (2CH^{Ar}), 77.6 (*C*^{Cq}-OH), 55.2 (OCH_3), 43.6 (CH_2), 37.1 (CH_2), 26.7 (CH_2), 23.1 (CH_2), 14.1 (CH_3); IR ($CHCl_3$): ν = 3483 (OH) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{24}NaO_2$ [*M* + Na]$^+$: 331.16685; found: 331.16781.

Procedure for the ring opening reaction of cyclobutenol 55. **Synthesis of α,β-unsaturated ketone 56**. A solution of cyclobutenol **55** (13 mg, 0.04 mmol), $[Rh(OH)(cod)]_2$ (0.002 mmol) and *rac*-BINAP (0.004 mmol) in toluene (0.2 mL) was heated under argon atmosphere in a sealed tube at 100 ºC for 3 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/toluene (1:1) to give ketone **56** (9 mg, 69%) as a colorless oil.

(*E*)-3-(4-Methoxyphenyl)-2-phenyloct-2-en-4-one 56. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.15 (m, 3H, 3CH^{Ar}), 7.05 (m, 2H, 2CH^{Ar}), 6.85 (m, 2H, 2CH^{Ar}), 6.67 (m, 2H,

2CH^{Ar}), 3.74 (s, 3H, OCH_3), 2.41 (t, 2H, *J* = 7.4 Hz, CH_2), 2.22 (s, 3H, CH_3), 1.57 (m, 2H, CH_2), 1.26 (m, 2H, CH_2), 0.86 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.2 (C=O), 158.4 (*C*$^{Ar\text{-}q}$-OCH_3), 142.1 (*C*=C), 140.2 (C$^{Ar\text{-}q}$), 138.9 (C$^{Ar\text{-}q}$), 131.0 (2CH^{Ar}), 128.7 (2CH^{Ar}), 127.9 (2CH^{Ar}), 126.8 (CH^{Ar}), 113.6 (2CH^{Ar}), 52.1 (OCH_3), 42.2 (CH_2), 26.0 2 (CH_2), 22.3 (CH_2), 22.2 (CH_3), 13.9 (CH_3); IR ($CHCl_3$): ν = 1685 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{25}O_2$ [*M* + H]$^+$: 309.18491; found: 309.18600.

Procedure for the dehydration reaction of cyclobutenol 55. **Synthesis of cyclobutadiene 57**. A solution of cyclobutenol **55** (13 mg, 0.04 mmol) in chloroform (0.8 mL) was heated at 100 °C under microwave irradiation for 3 h. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with hexanes/ethyl acetate (98:2) to give an *E*/*Z* mixture (87:13) of cyclobutadiene **57** (9 mg, 74%) as a colorless oil.

(*E*)-1-(4-Butylidene-2-phenylcyclobut-1-en-1-yl)-4-methoxybenzene 57. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.59 (m, 4H, 4CH^{Ar}), 7.06 (m, 3H, 3CH^{Ar}), 6.77 (m, 2H, 2CH^{Ar}), 5.56 (t, 1H, *J* = 7.5 Hz, =CH), 3.29 (s, 3H, OCH_3), 3.17 (s, 2H, CH_2), 2.15 (q, 2H, *J* = 7.3 Hz, CH_2), 1.46 (m, 2H, CH_2), 0.95 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 159.5 (*C*$^{Ar\text{-}q}$-OCH_3), 140.5 (*C*=C), 139.3 (*C*$^{Ar\text{-}q}$), 138.2 (*C*$^{Ar\text{-}q}$), 135.4 (*C*$^{Ar\text{-}q}$), 129.1 (2CH^{Ar}), 128.3 (2CH^{Ar}), 127.6 (CH^{Ar}), 126.3 (2CH^{Ar}), 114.1(2CH^{Ar}), 113.4 (=CH), 54.4 (OCH_3), 33.9 (CH_2), 30.3 (CH_2), 23.4 (CH_2), 13.7 (CH_3); IR (CH_2Cl_2): ν = 1620 (C=C) cm^{-1}.

Procedure for the addition reaction of phenylacetylene to cyclobutenone 46d. **Synthesis of cyclobutenol 58**. A cooled solution of *n*-BuLi (0.65 mmol) in hexanes (0.26 mL) was added dropwise to a stirred solution of phenylacetylene (56 mg, 0.55 mmol) in THF (8 mL) at 0 °C. After 30 min, the reaction was cooled to –78 °C and a solution of cyclobutenone **46d** (46 mg, 0.18 mmol) in THF (1 mL) was added dropwise. After 30 min, saturated ammonium chloride (1 mL) was added and the reaction mixture was allowed to warm to rt. Then, the mixture was extracted with ethyl acetate (3x10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave cyclobutenol **58** (48 mg, 76%) as a yellow oil.

2-(4-Methoxyphenyl)-3-phenyl-1-(phenylethynyl)cyclobut-2-en-1-ol 58. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (m, 2H, 2CH^{Ar}), 7.58 (m, 2H, 2CH^{Ar}), 7.49 (m, 2H, 2CH^{Ar}), 7.35 (m, 6H, 6CH^{Ar}), 6.94 (m, 2H, 2CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.36 (d, 1H, *J* = 12.6 Hz, C*H*H), 3.17 (d, 1H, *J* = 12.6 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 159.5 (*C*$^{Ar\text{-}q}$-OCH_3), 140.0 (*C*=C), 137.5 (*C*$^{Ar\text{-}q}$), 134.6 (*C*$^{Ar\text{-}q}$), 131.7 (2CH^{Ar}), 128.5 (CH^{Ar}), 128.4 (2CH^{Ar}), 128.3 (CH^{Ar}), 128.3 (2CH^{Ar}), 128.2 (2CH^{Ar}), 126.7 (2CH^{Ar}), 125.3 (C=*C*), 122.6 (*C*$^{Ar\text{-}q}$), 114.0 (2CH^{Ar}), 90.2 (*C*≡C), 84.3 (C≡*C*), 67.9 (*C*^{Cq}-OH), 55.2 (OCH_3), 46.5 (CH_2); IR ($CHCl_3$): ν = 3485 (OH) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{21}O_2$ [*M* + H]$^+$: 353.15361; found: 353.15250.

Procedure for the rearrangement reaction of cyclobutenol 58. **Synthesis of cyclohexa-2,5-dien-1-one 59**. A solution of cyclobutenol **58** (16 mg, 0.04 mmol) in toluene (0.2 mL) was heated at 140 °C under microwave irradiation for 15 min. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (93:7) to give cyclohexa-2,5-dien-1-one **59** (12 mg, 75%) as a colorless solid.

4''-Methoxy-5'-phenyl-[1,1':2',1''-terphenyl]-3'(6'*H*)-one 59. Mp 290–292 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.69 (m, 2H, $2CH^{Ar}$), 7.58 (s, 1H, =CH), 7.40 (m, 10H, $10CH^{Ar}$), 6.91 (m, 2H, $2CH^{Ar}$), 3.95 (d, 2H, 1.7 Hz, CH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 195.6 (C=O), 160.3 ($C^{Ar\text{-}q}$-OCH_3), 159.3 (*C*=C), 140.5 (C=*C*), 135.6 ($C^{Ar\text{-}q}$), 133.0 ($C^{Ar\text{-}q}$), 131.7 (=CH), 130.8 ($2CH^{Ar}$), 130.4 ($2CH^{Ar}$), 129.8 (CH^{Ar}), 129.4 (CH^{Ar}), 128.9 ($2CH^{Ar}$), 128.5 ($2CH^{Ar}$), 128.3 ($2CH^{Ar}$), 124.6 (*C*=C), 114.0 ($2CH^{Ar}$), 55.2 (OCH_3), 35.8 (CH_2); IR ($CHCl_3$): ν = 1670 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{21}O_2$ [*M* + H]$^+$: 353.15361; found: 353.15355.

Procedure for the Pd-catalyzed cross-coupling/rearrangement reaction of cyclobutenol 58. **Synthesis of cyclopent-3-en-1-one 60**. A solution of cyclobutenol **58** (34 mg, 0.1 mmol), iodobenzene (0.2 mmol), $Pd(OAc)_2$ (5 mol%) (0.005 mmol), PPh_3 (0.005 mmol), and Et_3N (0.25 mmol) in acetonitrile (26 mL/mmol) (2.5 mL) was heated in a sealed tube at 80 ºC for 1 h. The reaction mixture was allowed to cool to room temperature and was filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of AcOEt. The solution was concentrated under reduced pressure to afford the crude product, which was purified by column chromatography eluting with hexanes/ethyl acetate (95:5→9:1) to give cyclopent-3-en-1-one **60** (24 mg, 58%) as a yellow oil.

2-(Diphenylmethylene)-3-(4-methoxyphenyl)-4-phenylcyclopent-3-en-1-one 60. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.34 (m, 15H, $15CH^{Ar}$), 7.22 (m, 2H, $2CH^{Ar}$), 6.84 (m, 2H, $2CH^{Ar}$), 3.80 (s, 3H, OCH_3), 3.72 (s, 3H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 193.6 (C=O), 159.2 ($C^{Ar\text{-}q}$-OCH_3), 159.1 (*C*=C), 148.7 (C=*C*), 142.2 (*C*=C), 141.9 (C=*C*), 139.6 ($C^{Ar\text{-}q}$), 135.5 ($C^{Ar\text{-}q}$), 131.0 ($C^{Ar\text{-}q}$), 130.9 ($2CH^{Ar}$), 129.5 (CH^{Ar}), 129.4 ($2CH^{Ar}$), 129.0 ($2CH^{Ar}$), 128.4 ($4CH^{Ar}$), 128.2 ($2CH^{Ar}$), 128.1 (CH^{Ar}), 128.0 (CH^{Ar}), 127.8 ($2CH^{Ar}$), 124.7 ($C^{Ar\text{-}q}$), 113.8 ($2CH^{Ar}$), 55.2 (OCH_3), 37.0 (CH_2); IR ($CHCl_3$): ν = 1746 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{31}H_{25}O_2$ [*M* + H]$^+$: 429.18491; found: 429.18541.

Procedure for the spirocyclization reaction of cyclobutenol 58. **Synthesis of spirocyclic cyclobutene 61**. Molecular iodine (0.1 mmol) was slowly added to a stirred solution of cyclobutenol **58** (19 mg, 0.05 mmol) in nitromethane (1 mL). After 30 min at 40 °C, aqueous saturated $Na_2S_2O_3$ (1 mL) was added. Then, the mixture was extracted with ethyl acetate (3x10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave spirocycle **61** (26 mg, 85%) as a yellow oil.

2',3'-Diiodo-2-(4-methoxyphenyl)-3-phenylspiro[cyclobutane-1,1'-inden]-2-ene 61. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.68 (m, 2H, $2CH^{Ar}$), 7.38 (m, 6H, $6CH^{Ar}$), 7.20 (m, 1H, CH^{Ar}), 6.98 (m, 2H, $2CH^{Ar}$), 6.69 (m, 2H, $2CH^{Ar}$), 3.73 (s, 3H, OCH_3), 3.12 (d, 1H, *J* = 12.8 Hz, C*H*H), 3.02 (d, 1H, *J* = 12.8 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.3 ($C^{Ar\text{-}q}$-OCH_3), 145.2 (*C*=C), 144.9 (C=*C*), 139.0 ($C^{Ar\text{-}q}$), 137.9 ($C^{Ar\text{-}q}$), 134.7 ($C^{Ar\text{-}q}$), 128.5 ($2CH^{Ar}$), 128.3 (CH^{Ar}), 127.7 (CH^{Ar}), 127.4 ($2CH^{Ar}$), 126.6 (CH^{Ar}), 126.5 ($2CH^{Ar}$), 122.9 (CH^{Ar}), 122.0 (*C*=C), 121.7 (CH^{Ar}), 113.8 ($2CH^{Ar}$), 107.7 (C=*C*), 64.9 (C^{Cq}), 55.1 (OCH_3), 38.4 (CH_2); IR ($CHCl_3$): ν = 1642 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{22}I_2NO$ [*M* + NH_4]$^+$: 605.97853; found: 605.97945.

Procedure for the gold-catalyzed rearrangement reaction of cyclobutenol 58. **Synthesis of α,β-unsaturated ketone 62**. $Ph_3PAuNTf_2$ (0.0004 mmol) and methanol (0.04 mmol) were sequentially added to a stirred solution of cyclobutenol **58** (16 mg, 0.04 mmol)

in toluene (0.8 mL). After 15 min, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/diethyl ether (96:4) as eluent gave α,β-unsaturated ketone **62** (12 mg, 73%) as a yellow oil.

(*E*)-2-(2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-ylidene)-1-phenylethan-1-one 62. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.97 (m, 2H, $2CH^{Ar}$), 7.62 (m, 2H, $2CH^{Ar}$), 7.49 (m, 5H, $5CH^{Ar}$), 7.02 (m, 2H, $2CH^{Ar}$), 6.83 (s, 1H, =CH), 3.89 (s, 3H, OCH_3), 3.74 (s, 3H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 190.8 (C=O), 159.6 ($C^{Ar\text{-}q}$-OCH_3), 157.5 (*C*=C), 151.8 (C=*C*), 140.2 ($C^{Ar\text{-}q}$), 139.3 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 132.2 (CH^{Ar}), 129.9 (CH^{Ar}), 129.0 ($2CH^{Ar}$), 128.6 ($2CH^{Ar}$), 128.4 ($2CH^{Ar}$), 128.1 ($2CH^{Ar}$), 127.4 ($2CH^{Ar}$), 125.0 (*C*=C), 114.3 ($2CH^{Ar}$), 106.5 (=CH), 55.3 (OCH_3), 37.3 (CH_2); IR ($CHCl_3$): ν = 1691 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{21}O_2$ [*M* + NH_4]$^+$: 353.15361; found: 353.15513.

Procedure for the oxidation reaction of cyclobutenone 46u. **Synthesis of cyclobutenone 46u-O₂**. *m*-CPBA (0.20 mmol) was added to a stirred solution of cyclobutenone **46u** (20 mg, 0.08 mmol) in dichloromethane (1.6 mL) cooled at 0 °C. The reaction was stirred at 0 °C until disappearance of the starting material (TLC). Then, aqueous saturated $NaHCO_3$ (1 mL) was added to the reaction mixture before being extracted with dichloromethane (3x5 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave sulfone **46u-O₂** (14 mg, 62%) as a pale yellow solid.

3-(4-(Methylsulfonyl)phenyl)-2-phenylcyclobut-2-en-1-one 46u-O₂. Mp 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.04 (m, 2H, $2CH^{Ar}$), 7.92 (m, 2H, $2CH^{Ar}$), 7.67 (m, 2H, $2CH^{Ar}$), 7.43 (m, 3H, $3CH^{Ar}$), 3.72 (s, 2H, CH_2), 3.11 (s, 3H, SO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 187.3 (C=O), 158.4 (*C*=C), 144.3 ($C^{Ar\text{-}q}$), 142.3 ($C^{Ar\text{-}q}$), 142.3 ($C^{Ar\text{-}q}$), 137.3 ($C^{Ar\text{-}q}$), 129.7 (CH^{Ar}), 129.3 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 128.8 ($C^{Ar\text{-}q}$), 127.9 ($2CH^{Ar}$), 127.6 ($2CH^{Ar}$), 50.1 (CH_2), 44.3 (SO_2CH_3); IR ($CHCl_3$): ν = 1745 (C=O), 1384, 1097 (O=S=O) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{14}NaO_3S$ [*M* + Na]$^+$: 321.05559; found: 321.05656.

Procedure for the Wittig reaction of cyclobutenone 46u-O₂. **Synthesis of cyclobutene 63**. *t*-BuOK (0.46 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (0.46 mmol) in tetrahydrofuran (9 mL) cooled at 0 °C. The reaction was stirred for 30 min at 0 °C before cyclobutenone **46u-O₂** (70 mg, 0.23 mmol) was added. The reaction mixture was allowed to warm to rt and stirring was continued until disappearance of the starting material (TLC). Then, water (3 mL) was added to the mixture before being extracted with ethyl acetate (3x10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave cyclobutene **63** (42 mg, 63%) as a colorless solid.

1-(3-Methylene-2-phenylcyclobut-1-en-1-yl)-4-(methylsulfonyl)benzene 63. Mp 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.86 (m, 2H, $2CH^{Ar}$), 7.68 (m, 2H, $2CH^{Ar}$), 7.46 (m, 5H, $5CH^{Ar}$), 5.12 (=C*H*H), 4.85 (=CH*H*), 3.29 (s, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 144.3 (*C*=CH_2), 144.1 ($C^{Ar\text{-}q}$), 141.5 ($C^{Ar\text{-}q}$), 139.7 ($C^{Ar\text{-}q}$), 139.3 (*C*=C), 132.8 (C=*C*), 128.8 ($2CH^{Ar}$), 128.6 (CH^{Ar}), 127.6 ($2CH^{Ar}$), 127.5 ($2CH^{Ar}$), 127.0 ($2CH^{Ar}$), 100.4 (=CH_2), 44.5 (CH_2), 35.9 (SO_2CH_3); IR ($CHCl_3$): ν = 1379, 1098 (O=S=O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{16}NaO_2S$ [*M* + Na]$^+$: 319.07632; found: 319.07629.

VII.4. Notes and references

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VIII. CAPÍTULO 5

VIII.1. Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization *versus* Rare Bis(cyclization)

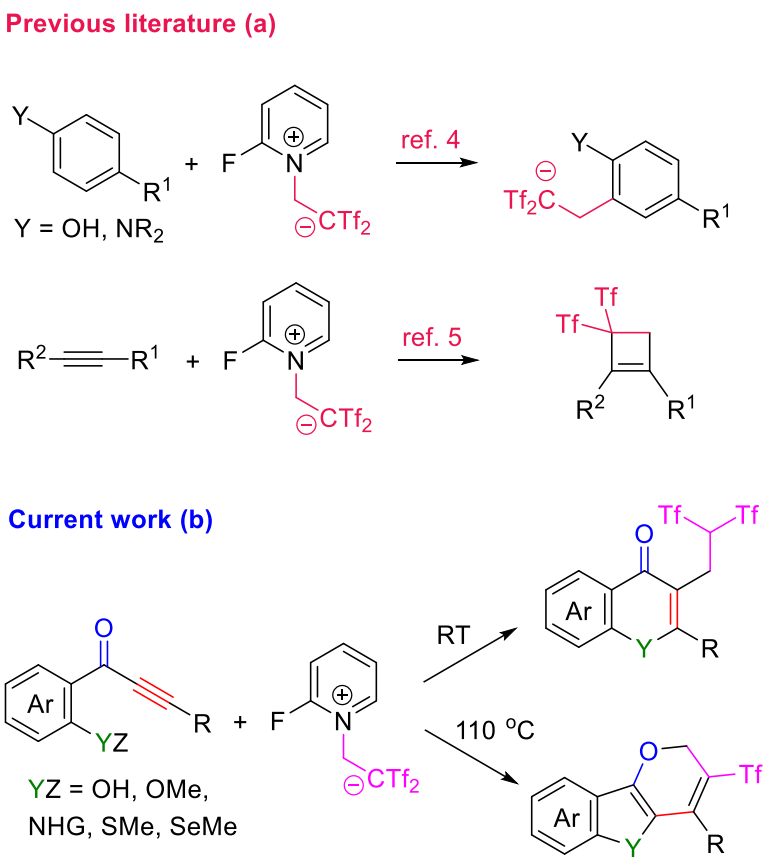
Functionalized ynones can be activated by $Tf_2C{=}CH_2$, which was generated in situ, to form zwitterionic species.These species were trapped in an intramolecular fashion by several nucleophiles to generate two major types of triflones in a divergent manner. Through fine-tuning of the reaction temperature, bis(triflyl)-6-membered- or (triflyl)-5-membered-fused-heterocycles were achieved in reasonable yields in a totally selective manner. In this way, bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones,(triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were constructed. Conceivable mechanistic pathways were suggested onthe basis of the isolation of several intermediates and the results from control experiments

Chem. Eur. J. **2018**, *24*, 8186

VIII.2. Article

VIII.2.1. Introduction

Tuning the selectivity in organic synthesis is difficult owing to the usual inherent preference for the creation of a specific type of product. In some cases, a divergent synthesis can be achieved through modification of the promoter, additive, and reagent. Consequently, the discovery of novel strategies for divergent reactions is appealing. Ynones, versatile acetylenic platforms that are readily available from the reaction of acyl chlorides and metal acetylides, have great potential for synthetic applications in nucleophilic additions, cycloadditions, and condensation reactions.[1, 2] However, to date, less conventional reactivities are underexplored. The presence of fluoroorganic moieties in organic compounds notably influences the physicochemical[3] and pharmacological properties of the fluorinated derivatives. Particular attention has been paid to the strongly electron-withdrawing triflyl functionality, which exhibits a mild lipophilicity and subsequent improvement in bioavailability. In this context, the group of Yanai has recently developed an innovative methodology that discloses the use of 2-(pyridinium-1-yl)-1,1-bis(perfluoroalkylsulfonyl)ethan-1-ides as a stable source of $Tf_2C{=}CH_2$,[4] whereas we have developed a route for the preparation of bis(triflyl)cyclobutenes[5] (Scheme VIII.1a). On the basis of these previous observations, we decided to study the reactivity of functionalized ynones. Unexpectedly, divergent reaction paths, with respect to previous results, were encountered. A detailed study of this chemistry unveiled novel aspects of the unique reactivity of ynones, which allowed the direct preparation of various heterocyclic cores that were decorated with fluorinated moieties (Scheme VIII.1b).

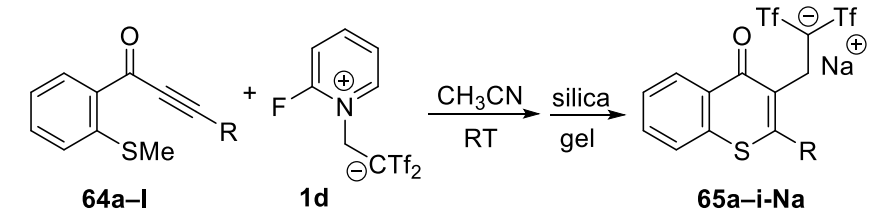


Scheme VIII.1. Background and current design for the synthesis of triflones from 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide.

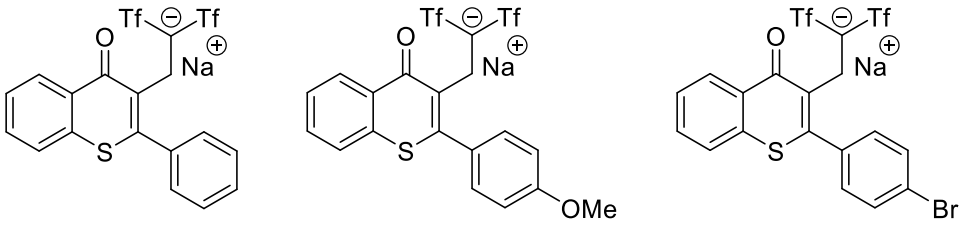
VIII.2.2. Results and discussion

To determine the feasibility of using ynones as precursors, 1-[2-(methylthio)phenyl]-3-phenylprop-2-yn-1-one **64a**[2a] was treated with 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** in acetonitrile at room temperature. Interestingly, the formation of bis(triflyl)thioflavone **65a** was observed (Scheme VIII.2) rather than Friedel–Crafts-type bis(triflyl)alkylation or cyclobutene construction (Scheme VIII.1). Notably, a C−S bond,[6] which is present in a vast array of natural products and bioactive molecules, such as thioflavones, was formed under mild conditions. The organofluorine substituent was also incorporated in the same step under metal-free conditions through dual functionalization of the alkyne moiety. With these cyclization conditions in hand, we examined the scope of MeS-functionalized ynones that were susceptible to thioflavone generation. The scope and limitations were initially evaluated through different substitution patterns

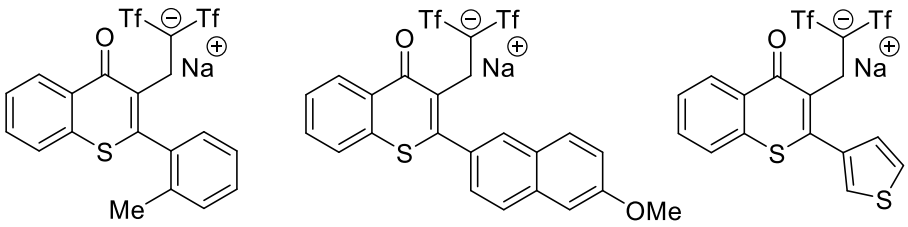
at the alkyne terminus. Accordingly, various substituents on the aromatic ring at the terminal alkyne, such as methoxy, methyl, and bromo were well tolerated, and the desired fluorinated thioflavones **65a–d** were isolated in yields of 41 to 77% (Scheme VIII.2). Furthermore, naphthalene-, indole-, thiophene-, and ferrocene-linked alkynes **64e–i** also underwent the thiacyclization/functionalization sequence (Scheme VIII.2).



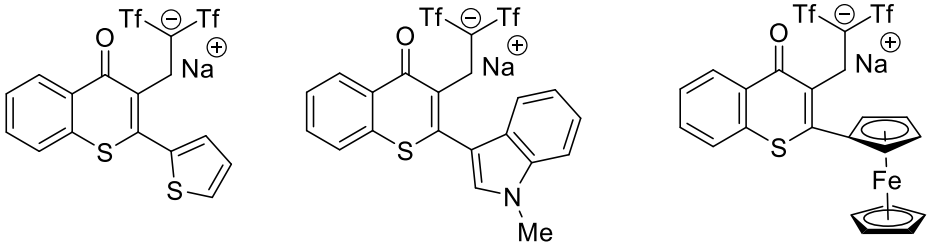
64a–l **1d** **65a–i-Na**



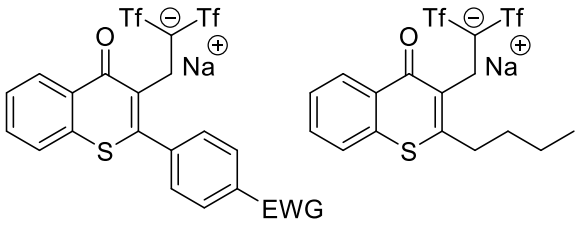
65a-Na (41%, 5 h) **65b-Na** (70%, 1 h) **65c-Na** (39%, 7 h)



65d-Na (74%, 2 h) **65e-Na** (77%, 3 h) **65f-Na** (67%, 2 h)



65g-Na (57%, 1 h) **65h-Na** (64%, 2 h) **65i-Na** (39%, 1 h)

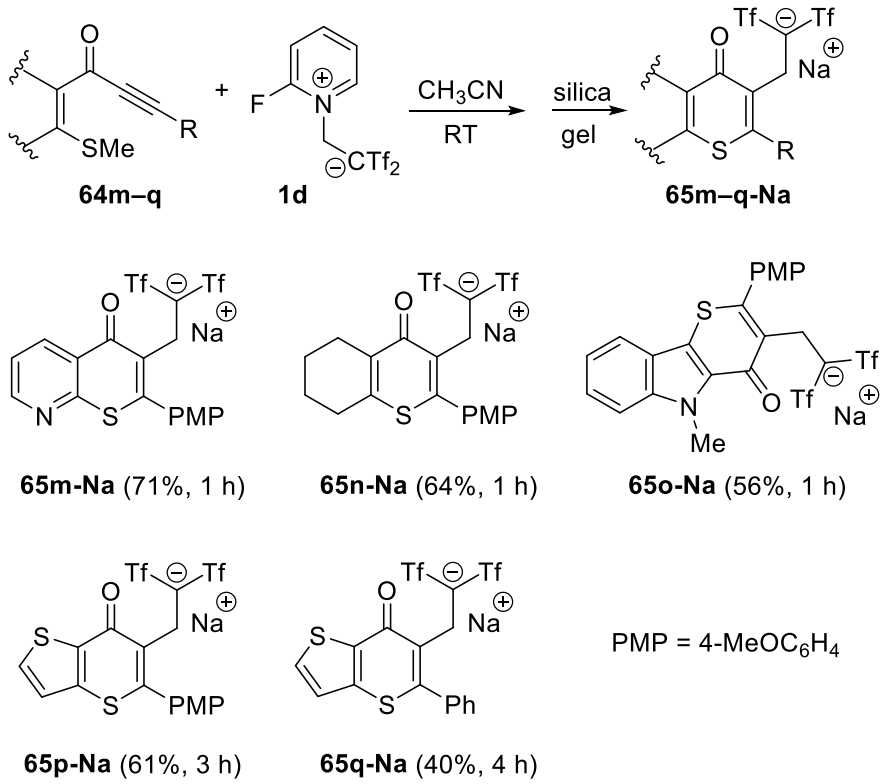


65j-Na (EWG = NO_2, 0%, 24 h) **65l-Na** (0%, 24 h)
65k-Na (EWG = CF_3, 0%, 24 h)

Scheme VIII.2. Controlled preparation of bis(triflyl)thioflavones **65a–i**.

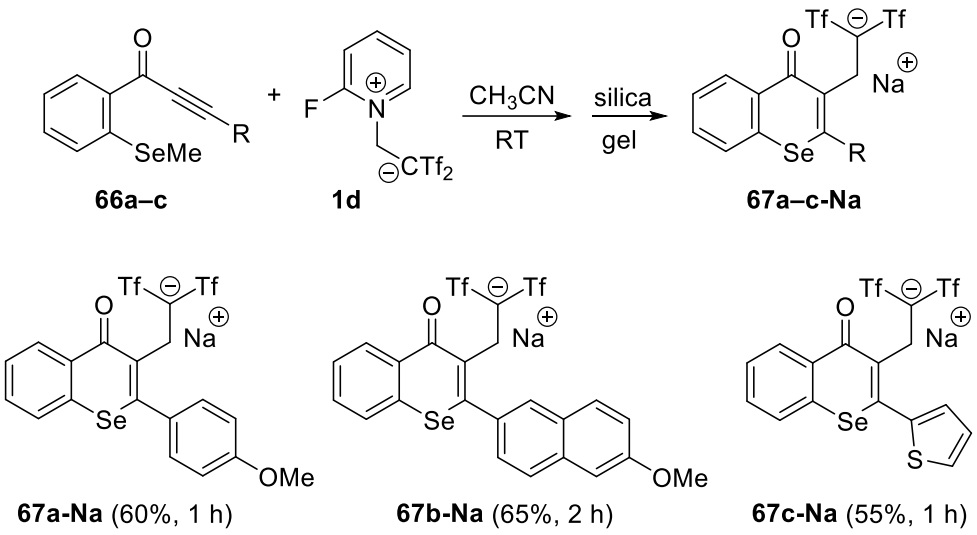
Notably, products **65a–i** easily dissociate the acidic hydrogen atom to provide the corresponding metal salts **65a–i-Na** after column chromatography.[7] Unfortunately, the highly deactivating 4-$NO_2C_6H_4$ and 4-$CF_3C_6H_4$ moieties that were attached to the alkyne group did not afford the corresponding thioflavones **65j** and **65k**, and alkynones that bore an alkyl substituent on the alkyne, such as alkyne **64l**, were also inert in the presence of zwitterion **1d**.

The scope of the reaction was also explored through modification of the MeS–alkynone tether. Variation of the benzene linker was viable, with pyridine-, cyclohexene-, indole-, and thiophene-tethered alkynones all affording the desired organofluorine thioflavones **65m–q** in reasonable yields (Scheme VIII.3).



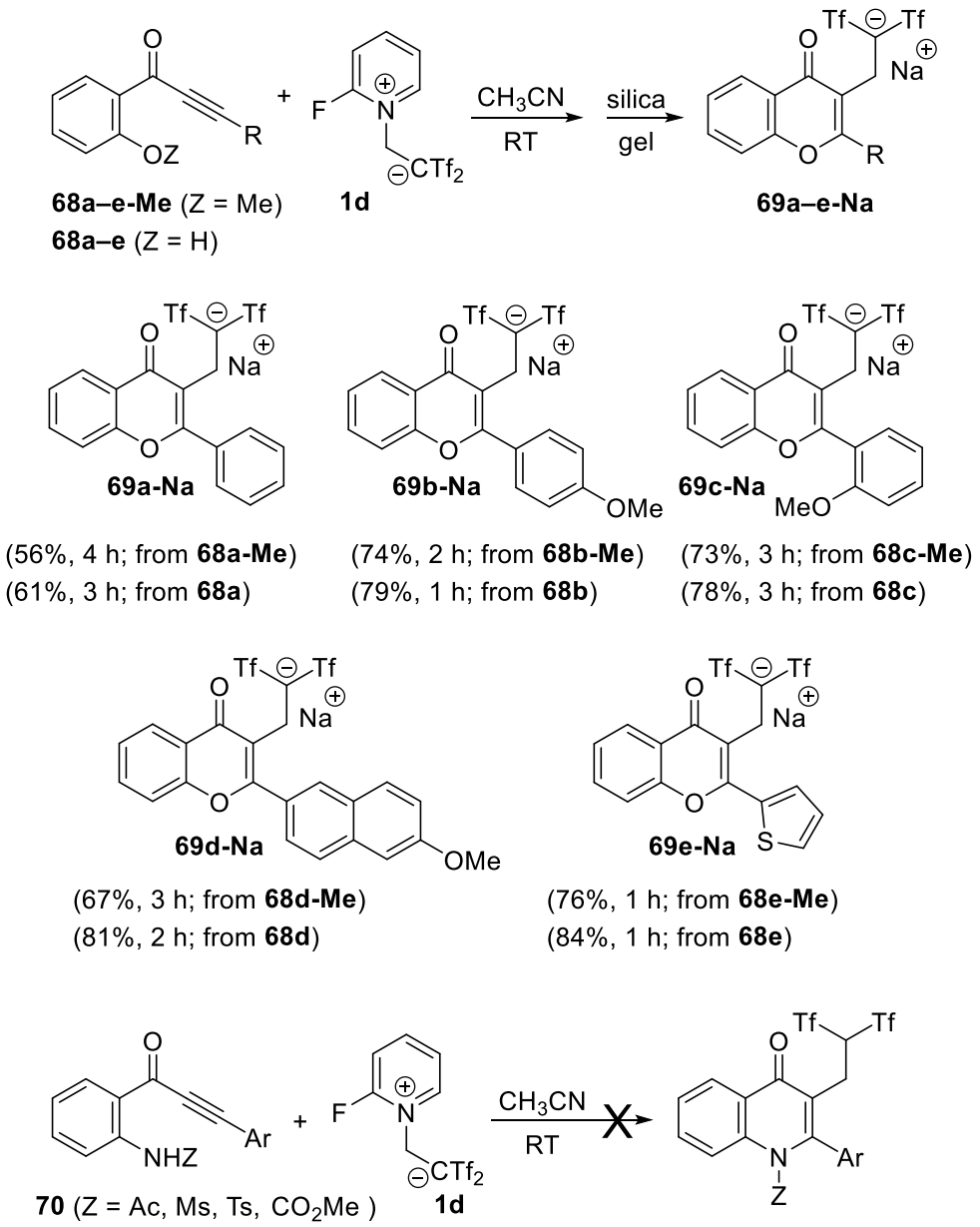
Scheme VIII.3. Controlled preparation of bis(triflyl)thioflavones **65m–q**.

Taking into account the rich chemistry and the important biological properties of organoselenium compounds, the scope of the nucleophile was investigated by replacing the SMe group for an SeMe moiety. Noticeably, the reactions of (methylseleno)-alkynones **66a–c** and zwitterion **1d** smoothly gave the desired fluorinated selenoflavones **67a–c** as the exclusive products (Scheme VIII.4).



Scheme VIII.4. Controlled preparation of bis(triflyl)selenoflavones **67a–c**.

The nature of the nucleophile could also be modified to oxygen-substituted derivatives. Accordingly, methoxyalkynones **68a–e-Me** and hydroxyalkynones **68a–e** were both found to be suitable cyclization precursors, and bis(triflyl)flavones **69a–e** were accomplished in yields ranging from 56 to 84% (Scheme VIII.5).

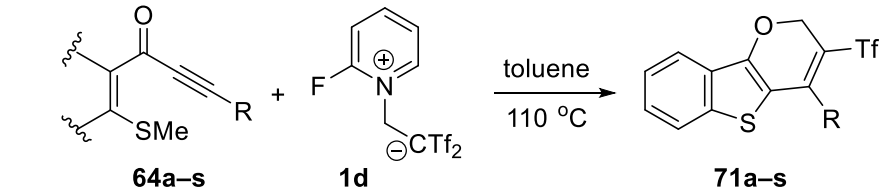


Scheme VIII.5. Controlled preparation of bis(triflyl)flavones **69a–e**.

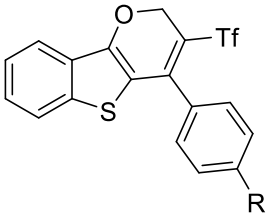
Unfortunately, the amide functionality in HN−Ac-, HN−Ms-, HN−Ts-, and HN−CO_2Me-substituted amido alkynones 8 was unreactive under the above conditions, which prevented access to fluorinated quinolin-4-one derivatives. Notably, the signal that corresponded to the highly acidic hydrogen on the alpha-carbon atom (Tf_2CH) was not observed in the ^{1}H NMR spectra of compounds **65**, **67**, and **69**, which was attributed to chromatographic purification without re-acidification. Ishihara et al. reported that the purification of strongly acidic compounds by column chromatography on silica gel gives the corresponding calcium salts.[7a] Yanai also

reported that Tf_2CH bearing compounds were strongly acidic and eluted as the corresponding Ca^{2+} salts during silica gel chromatography.[7b] In our case, the metal cation is sodium in accordance with our previous report of a related cyclobutenyl-$[Tf_2CCH_2]^-Na^+$ derivative, which was structurally defined by X-ray crystallographic analysis.[5c] In addition, sodium was detected in representative flavone derivatives, such as **65m-Na**, **67c-Na**, and **69b-Na**, through the use of two different analytical techniques, namely SEM-EDX and ^{23}Na NMR.

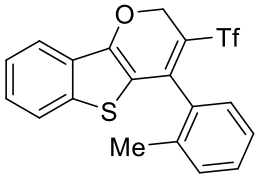
Having probed the feasibility of this cyclization/functionalization sequence and tested several structural variations within the acyclic precursors, investigations into a tunable reactivity were initiated by testing variations in the reaction solvent and temperature. Initially, MeS-alkynone **64a** was treated with zwitterion **1d** in acetonitrile at 80ºC, which resulted in a mixture (2:1) of bis(triflyl)thioflavone **65a** and 3-[(trifluoromethyl)sulfonyl]-2H-benzo[4,5]thieno[3,2-b]pyran **71a**. With this promising result in hand, we hoped that fine tuning of the reaction conditions might result in the sole construction of tricycle **71a**. Zwitterion **1d** is almost insoluble in apolar or halogenated solvents at RT, but it can be used in these solvents when they are heated at reflux. Replacing acetonitrile with other solvents was found to be useful; to our satisfaction, the addition of zwitterion **1d** to a boiling solution of alkynone **64a** in toluene gave the tricycle **71a** exclusively, without any trace of bicycle **65a** (Scheme VIII.6). Noticeably, simple temperature and solvent alterations gave rise to the divergent formation of two entirely distinct fluorinated heterocyclic cores from a common cyclization precursor.



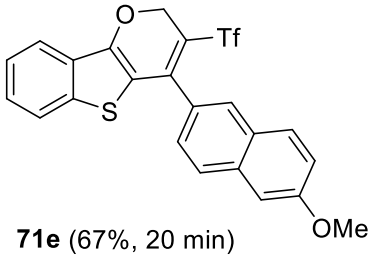
64a–s **1d** **71a–s**



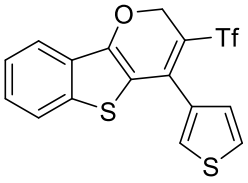
71a (R = H, 53%, 15 min)
71b (R = OMe, 82%, 10 min)
71c (R = Br, 56%, 15 min)



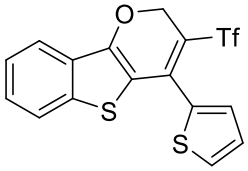
71d (75%, 15 min)



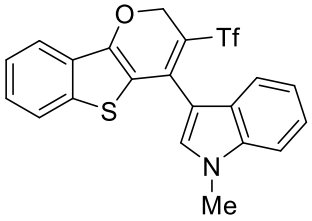
71e (67%, 20 min)



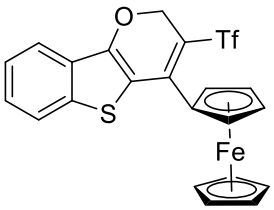
71f (64%, 20 min)



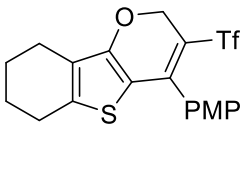
71g (71%, 10 min)



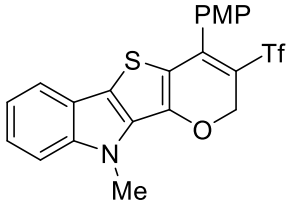
71h (76%, 15 min)



71i (22%, 10 min)[a]

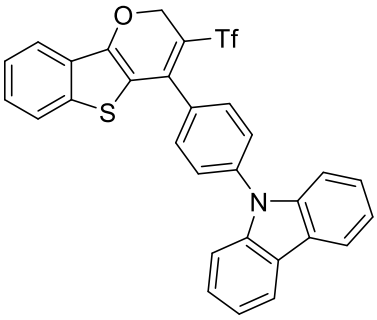


71n (71%, 15 min)

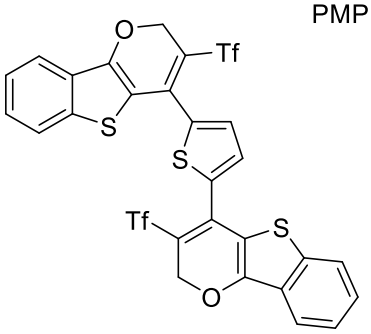


71o (55%, 15 min)

PMP = 4-MeOC$_6$H$_4$



71r (65%, 10 min)



71s (77%, 15 min)

Scheme VIII.6. Controlled preparation of tricyclic triflylbenzothienopyrans **71**. [a] Partial decomposition during chromatographic purification.

This second domino process allowed the direct metal-free access to a tricyclic framework with the simultaneous formation of C−S, C−O, and C−C bonds. A variety of MeS-alkynones **64** that contained various functional groups and tethers were also submitted to bis(cyclization). As a result, various fused thieno[3,2-*b*]pyrans **71** were achieved with exquisite selectivity in reasonable yields, with the exception of ferrocene derivative **71i**, which was obtained in a reduced yield of 22% (Scheme VIII.6). The reaction was even extended to the symmetrical bis(MeS-alkynone) **64s**, with which a two-fold sequence took place to afford benzothiophene-linked bis(tricycle) **64s** (Scheme VIII.6). To the best of our knowledge, a general access to fused tricyclic benzothienopyrans from acyclic precursors in one synthetic operation has not yet been reported. The structure of tricycle **71a** was confirmed by X-ray crystallography (Figure VIII.1).[8]

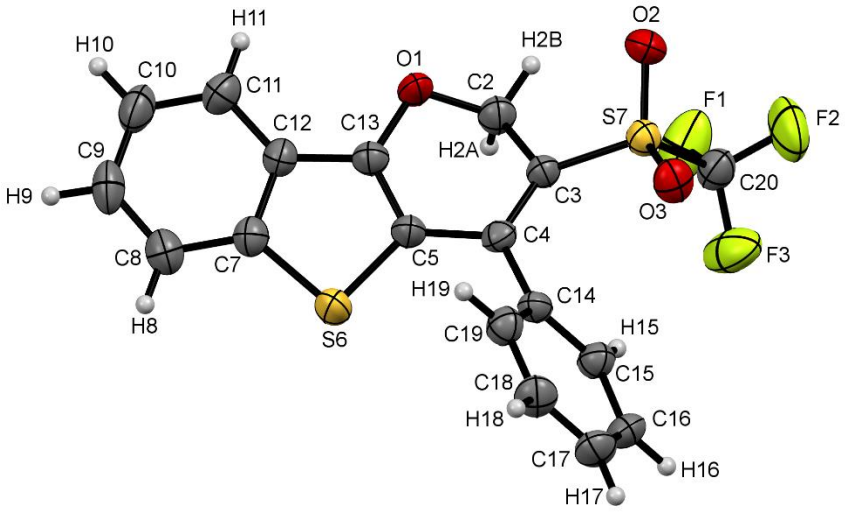
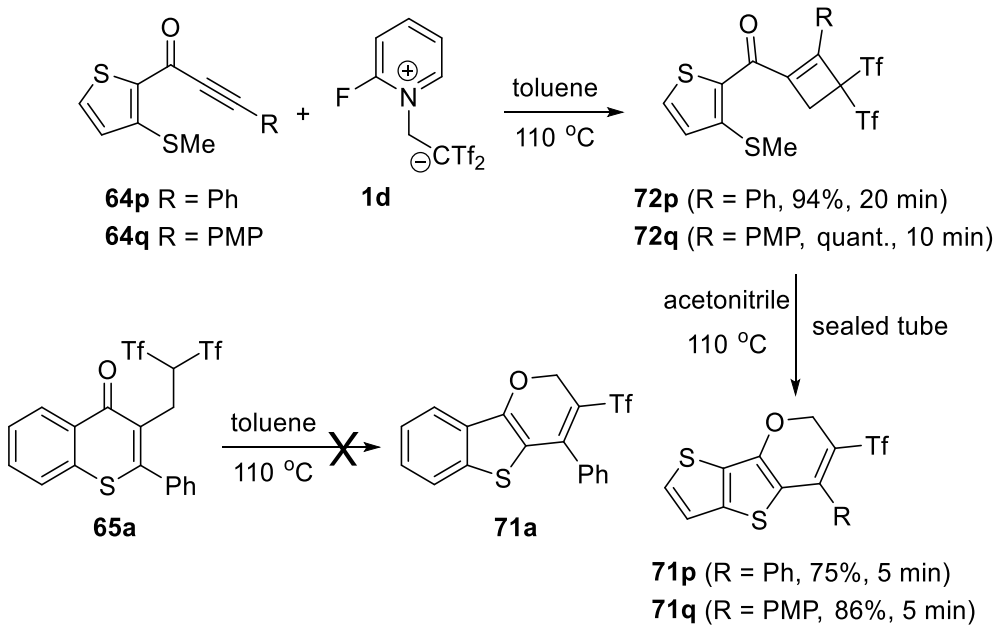


Figure VIII.1. ORTEP drawing of 3-[(trifluoromethyl)sulfonyl]-2H-benzo[4,5]thieno[3,2-b]pyran **71a**. Thermal ellipsoids shown at 50% probability.

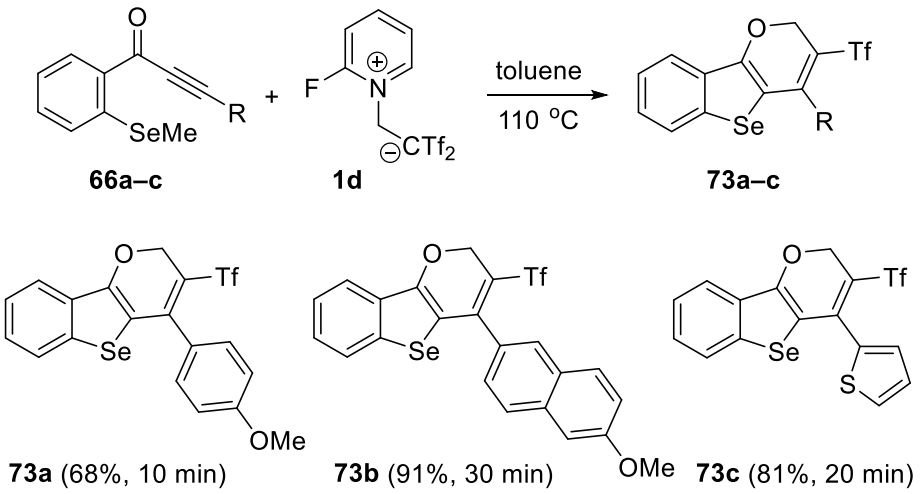
We conceived that bicycles of type **65** could be converted into fused tricycles **71** at elevated temperature. However, the treatment of a toluene solution of bicycle **65a** at 110ºC gave no reaction. Even more puzzling was the formation of cyclobutenes **72p** and **72q** in almost quantitative yields from thiophenetethered MeS-alkynones **64p** and **64q**, respectively, under the optimized conditions for the formation of tricycles **71**. Fortunately, heating an acetonitrile solution of cyclobutenes **72p** and **72q** in a sealed tube at 110ºC resulted in full conversion to 6-(triflyl)-7*H*-thieno[2',3':4,5]thieno[3,2-*b*]pyrans **71p** and **71q**, respectively (Scheme VIII.7).

Therefore, it may be inferred that cyclobutenes **72** and not bicycles **65** are intermediates in the formation reaction of fused pyrans **71**.



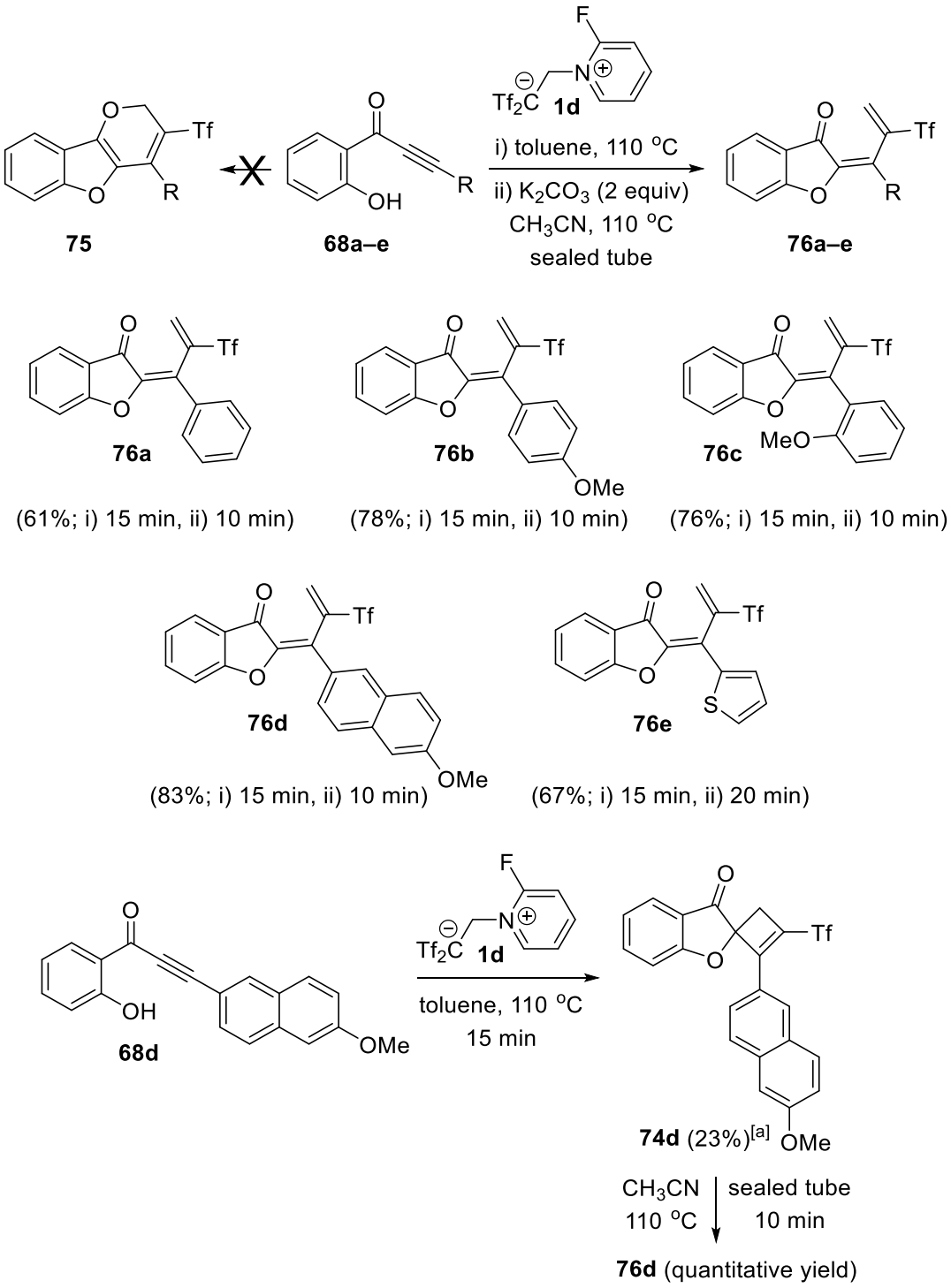
Scheme VIII.7. Controlled preparation of bis(triflyl)cyclobutenes **72p**, **72q** and triflyl(bis-thieno)pyrans **71p**, **71q**.

It was important to extend the current method for the synthesis of tricyclic thienopyrans to other relevant heterocyclic cores. For example, replacement of the S atom for a bulkier Se normally increases the semiconducting properties of the resultant less aromatic selenophenes in comparison with their thiophene counterparts. We initiated our study by using (methylselanyl) phenyl-propynones **66a–c** as the alkynone partner; gratifyingly, the use of heat did allow the efficient synthesis of 3-(triflyl)-2*H*-benzo[4,5]selenopheno[3,2-*b*]pyrans **73a–c** (Scheme VIII.8). Consequently, MeSe-alkynones were proven to be excellentsubstrates for the bis(cyclization), because changing the heteroatom from S to Se has no effect on the reactivity pattern of the compound.



Scheme VIII.8. Preparation of triflylbenzoselenophenopyrans **73**.

The reaction of zwitterion **1d** with substrates **68-Me**, which contain a methoxy substituent ortho to the alkynone group, in toluene at 110ºC gave rise to an intractable mixture of products. A beneficial effect was provoked by using hydroxyalkynone substrates **68** instead. The treatment of hydroxyalkynones **68** with zwitterion **1d** in boiling toluene did not allow a direct preparation of the expected tricycles; instead, several unstable products were formed. Interestingly, in one case, we were able to isolate a putative intermediate, namely, spirocyclic cyclobutene **74d** (Scheme VIII.9). Fortunately, the reaction of hydroxyalkynones **68** was found to be successful in the presence of a base, which probably enhanced the nucleophilicity of the oxygenated functionality. Among several bases tested, potassium carbonate provided the best results. In this way, hydroxyalkynones **68a–e** suffered a rearrangement reaction to form adducts **76a–e** (Scheme VIII.9).



Scheme VIII.9. Controlled preparation of triflylallylidenebenzofuranones **76a–e** and spirocyclic cyclobutene **74d**. [a] Partial decomposition during chromatographic purification.

Surprisingly, the expected tricycles **75** were not obtained. Instead, compounds **76** were formed, which bear an open-chain conjugated dienone structure, as confirmed by X-ray diffraction analysis of compound **76e** (Figure VIII.2)[9].

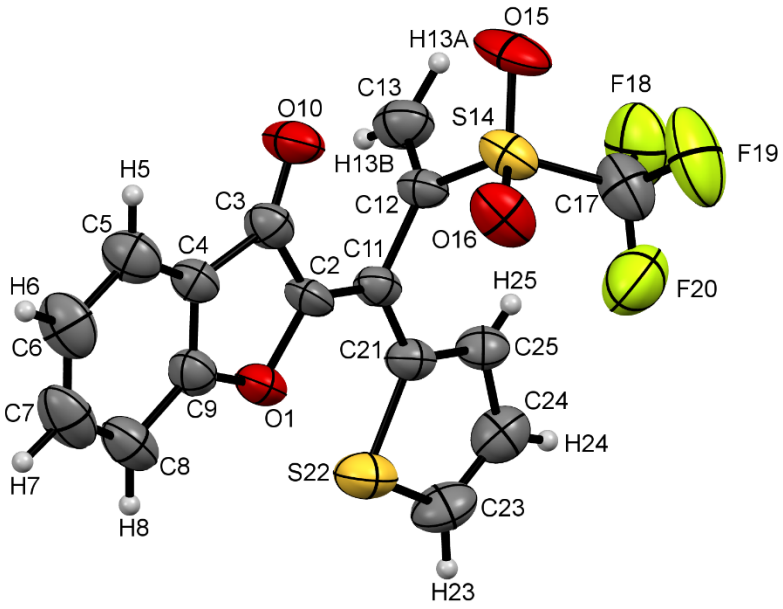
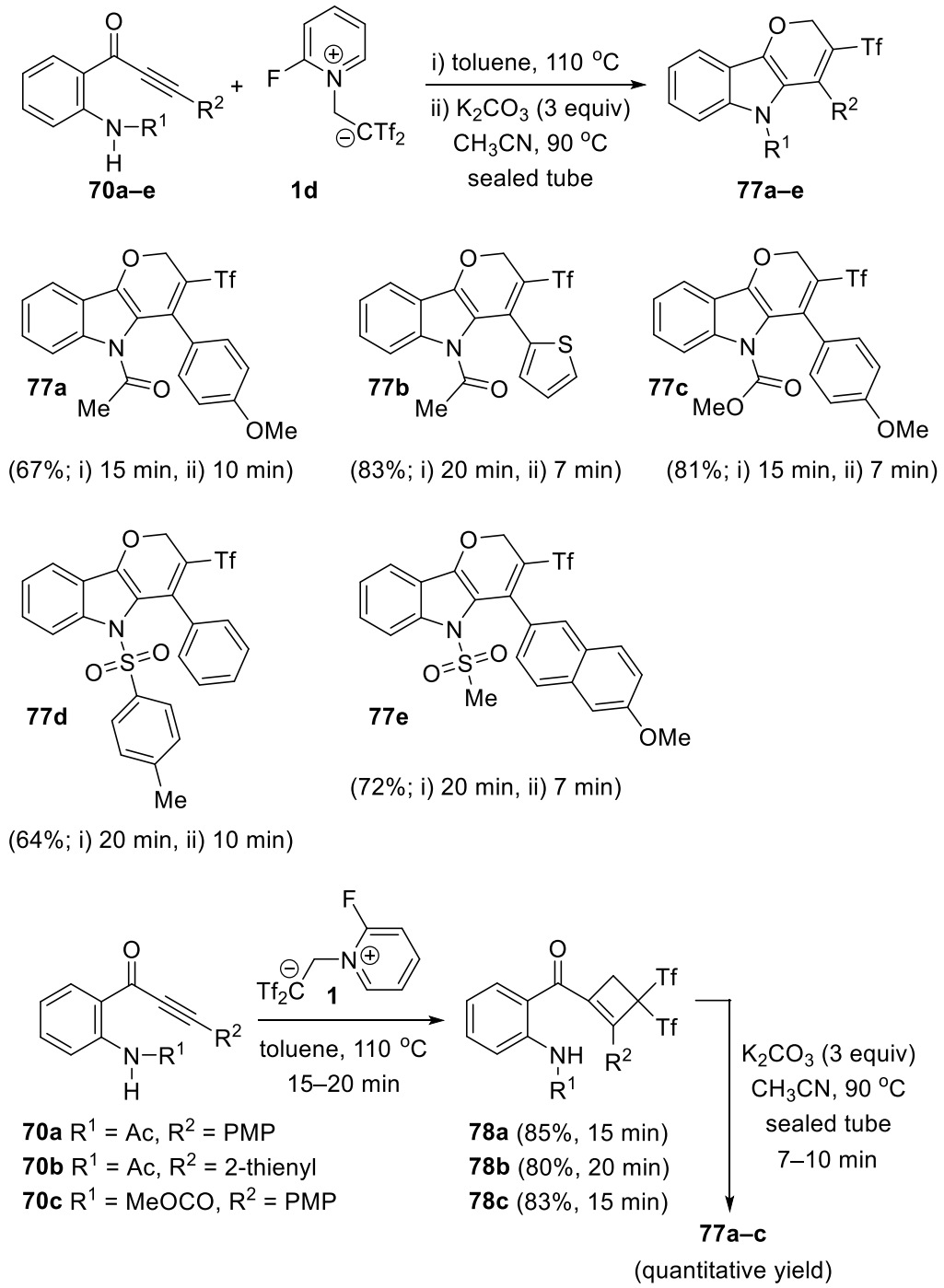


Figure VIII.2. ORTEP drawing of (*E*)-2-(1-(thiophen-2-yl)-2-((trifluoromethyl)sulfonyl) allylidene)benzofuran-3(2*H*)-one **76e**. Thermal ellipsoids shown at 50% probability.

The occurrence of such an unanticipated result could be tentatively explained by bond lengths: the C−S and the C−Se bonds are longer than the C−O bond, which may disfavor the final cyclization in this latter case. Interestingly, adducts **76** are (triflyl)vinyl aurones, a group of flavonoids. When the proposed intermediate **74d** was heated in acetonitrile at 110ºC in a sealed tube, compound **76d** was formed (Scheme VIII.9); this confirmed that spirocyclic cyclobutene species **74** is an intermediate in our cyclization reaction.

Next, we used amido alkynone substrates **70** with the intention of preparing fused indoles. However, no reaction proceeded in the presence of zwitterion **1d** at room temperature. Fortunately, under similar conditions to those developed for the preparation of functionalized aurones **76**, various azatricycles **77** were obtained in synthetically valuable yields (Scheme VIII.10).



Scheme VIII.10. Controlled preparation of triflyl-2,5-dihydropyrano[3,2-*b*]indoles **77a–e** and cyclobutenes **78a–c**.

Therefore, both heat and the presence of a base are crucial for the success of the cyclization/rearrangement sequence. The PMP group in product **77a** was be replaced with a naphthyl, thienyl, or phenyl group without attenuation in reaction efficiency. Furthermore, our protocol accommodated different N-protected functional

groups, which included acetamides and sulfonamides. The tricyclic structure of 2,5-dihydropyrano[3,2-*b*]indole **77b** was confirmed by X-ray diffraction analysis (Figure VIII.3).[10]

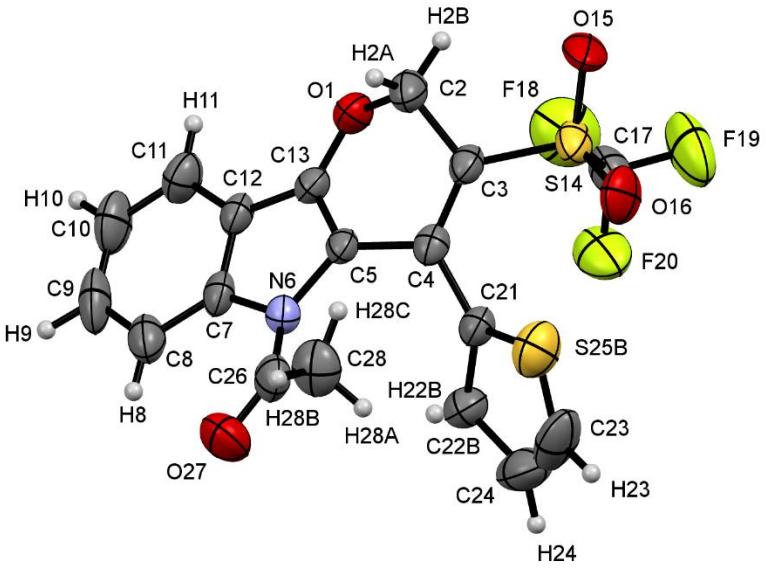
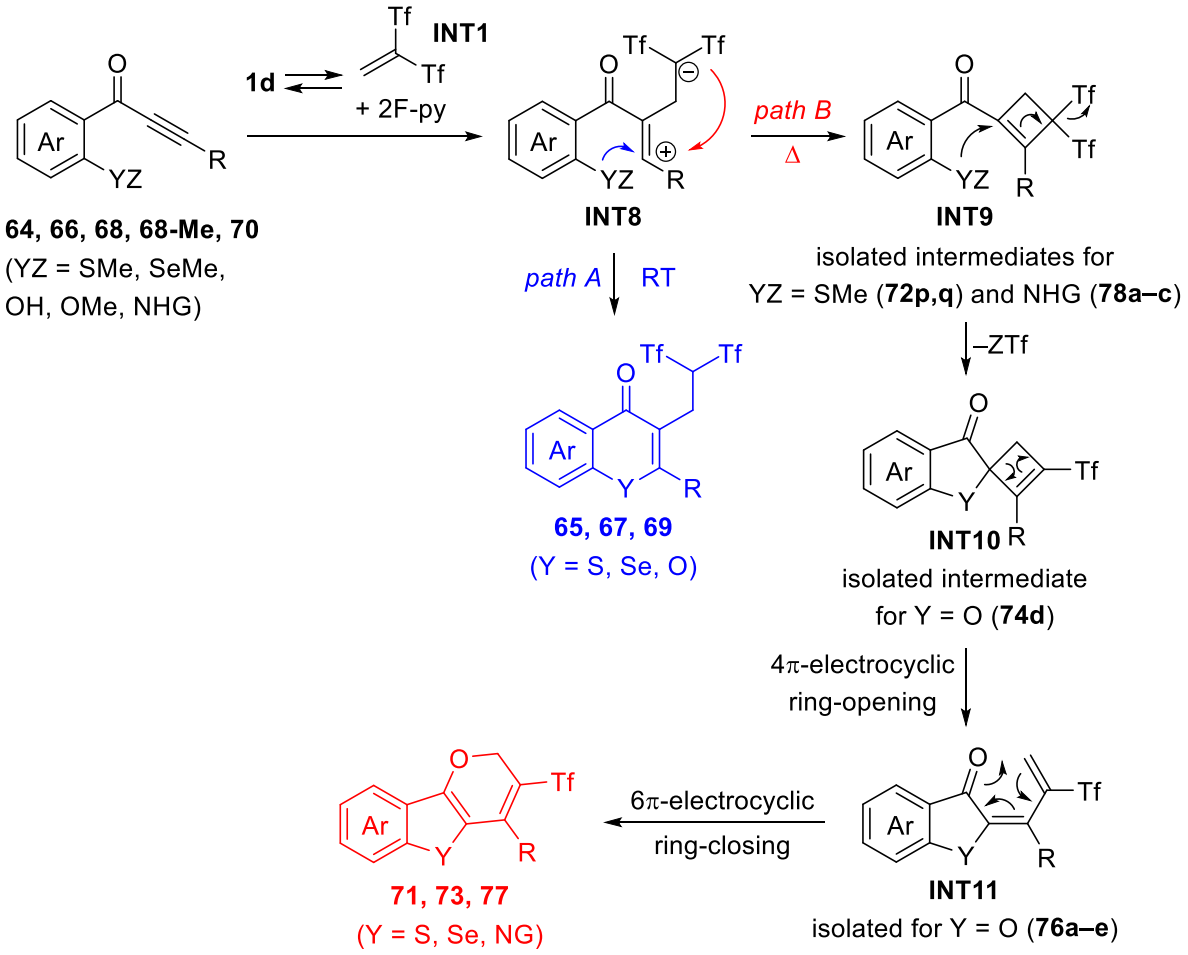


Figure VIII.3. ORTEP drawing of 1-(4-(thiophen-2-yl)-3-((trifluoromethyl)sulfonyl)-pyrano[3,2-b]indol-5(2*H*)-yl)ethan-1-onev **77b**. Thermal ellipsoids shown at 50% probability.

To obtain direct evidence of a cyclobutene-type intermediate, the reactions between amido alkynones **70a–c** and zwitterion **1d** were carried out at 110ºC with suppression of the base treatment. Pleasingly, we isolated cyclobutene derivatives **78a–c** in good yields, and thermal treatment of these strained intermediates in acetonitrile under basic conditions (K_2CO_3) resulted in the formation of tricycles **77a-c** (Scheme VIII.10), which suggests that adducts **78** are key intermediates.

A possible pathway for the metal-free formation of bicyclic triflones **65**, **67**, and **69** is outlined in Scheme VIII.11. Formation of 1,1-bis((trifluoromethyl)sulfonyl)ethene **INT1** from 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** would trigger a nucleophilic attack of the C2 atom of propynones **64**, **66**, and **68** onto the terminal carbon atom of alkene **INT1**. The so formed zwitterionic species **INT8** would suffer a selective intramolecular heterocyclization to generate bicycles **65**, **67**, and **69** (path A). From common intermediate **INT8**, we have postulated an alternative path that involves a carbocyclization reaction to generate intermediate cyclobutenes **INT9** (path B). This alternative cyclobutene formation is not achievable at RT.

Subsequently, the regioselective nucleophilic addition of a -SMe, -SeMe, -OH, or -NHP functional group to the C1 atom of bis((trifluoromethyl)-sulfonyl)cyclobut-1-en-1-yl)methanones **INT9** occurs to form spirocyclic cyclobutene intermediates **INT10**. Subsequent rearrangement with cyclobutene ring-opening gives rise to dienone intermediates **INT11**. Final 6π-electrocyclic ring closure affords tricyclic triflones **71**, **73**, and **77**. This second path must be driven by alleviation of the ring strain linked to the cyclobutene moiety upon formation of the deeply conjugated dienone intermediates **INT11**. Although the obtainment of cyclobutenes **72p**, **72q** (Scheme VIII.7) and **78a–c** (Scheme VIII.10), spirocyclic cyclobutene **74d** (Scheme VIII.9), and dienones **76a–e** (Scheme VIII.9) was serendipitous, these findings are in agreement with the mechanism of Scheme VIII.11, because detectable intermediates were isolated.



Scheme VIII.11. Rationalization for the formation of bicyclic triflones **65**, **67**, **69** and tricyclic triflones **71**, **73**, **77**.

VI.2.3. Conclusion

We have unveiled the reaction of $Tf_2C{=}CH_2$ with ynones, which gives rise to a divergent preparation of two major triflonebased products. The selectivity of the product can be completely switched through the adjustment of the reaction temperature. In this way, bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were constructed. On the basis of control experiments and the trapping of several intermediates, we have proposed two conceivable reaction mechanisms.

VI.3. Experimental Section

General methods: NMR spectra were recorded at 25 ºC on a 300 MHz instrument: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on a QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES). All reported compounds are racemic. All commercially available compounds were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.00 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 77.0 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or acetone-d_6 (^{1}H, 2.00 ppm; ^{13}C, 206.3 ppm), or CD_3CN (^{1}H, 2.00 ppm; ^{13}C, 118.2 ppm). Chemical shifts in ^{19}F are given in ppm relative to (trifluoromethyl)benzene ($C_6H_5CF_3$) in $CDCl_3$ (^{19}F, -63.7 ppm). Chemical shifts in ^{77}Se are given in ppm relative to PhSeSePh in $CDCl_3$ (^{77}Se, 0.00 ppm). Chemical shifts in ^{23}Na are given in ppm relative to NaCl in D_2O (^{23}Na, 0.00 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. The Energy Dispersive X-ray (EDX) microanalysis was performed on a JEOL-JEM-2010 microscope. Column chromatography was carried out using silica gel 60, 0.04-0.06 mm, for flash chromatography (230-400 mesh ASTM) provided by Scharlau. All commercially available compounds were used without further purification.

General procedure for the reaction between alkynones 64a–q, 66a–c, 68a–e, and 68a–e-Me with pyridinium salt 1d at room temperature. Preparation of bis(triflyl)thioflavones 65a-Na – 65i-Na, 65m-Na – 65q-Na, bis(triflyl)selenoflavones 67a-Na – 67c-Na, and bis(triflyl)flavones 69a-Na – 69e-Na. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1** (0.2 mmol) was added at room temperature to a solution of the appropriate alkynone **64a–q**, **66a–c**, **68a–e**, and **68a–e-Me** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures followed by further disolution in Et_2O, precipitation with hexanes and filtration, gave analytically pure compounds. Spectroscopic and analytical data for adducts **65a-Na – 65i-Na, 65m-Na – 65q-Na, 67a-Na – 67c-Na,** and **69a-Na – 69e-Na** follow.

Bis(trifluoromethylsulfonyl)thioflavone 65a-Na. From 20 mg (0.08 mmol) of alkynone **64a**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65a-Na** (18 mg, 41%) as a colorless solid; mp 316–318ºC; ^{1}H NMR (500 MHz, acetone-d_6, 25 ºC): δ = 8.45 (d, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.66 (m, 2H, $2CH^{Ar}$), 7.52 (m, 1H, CH^{Ar}), 7.42 (s, 5H, $5CH^{Ar}$), 3.67 (s, 2H, CH_2); ^{13}C NMR (125 MHz, acetone-d_6, 25 ºC): δ = 181.3 (C=O), 151.4 (S-*C*=C), 138.3 ($C^{Ar\text{-}q}$), 137.6 ($C^{Ar\text{-}q}$), 132.9 (S-C=*C*), 132.3 (CH^{Ar}), 131.9 ($C^{Ar\text{-}q}$), 130.5 ($2CH^{Ar}$), 130.1 (CH^{Ar}), 129.7 (CH^{Ar}), 129.0 ($2CH^{Ar}$), 128.1 (CH^{Ar}), 126.5 (CH^{Ar}), 122.9 (q, J_{CF} = 327.7 Hz, $2CF_3$), 63.9 (CTf_2), 28.1 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –80.6 (s, 6F, $2CF_3$); IR (acetone): ν = 1732 (C=O), 1381, 1109 (O=S=O), 1211 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{13}F_6O_5S_3$ [*M* + H]$^{+}$: 530.98238; found: 530.98432.

Bis(trifluoromethylsulfonyl)thioflavone 65b-Na. From 40 mg (0.14 mmol) of alkynone **64b**, and after flash chromatography of the residue using hexanes/ethyl acetate

(1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65b-Na** (57 mg, 70%) as a colorless solid; mp 219–221ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.51 (m, 1H, CH^{Ar}), 7.73 (m, 2H, $2CH^{Ar}$), 7.60 (m, 1H, CH^{Ar}), 7.32 (m, 2H, $2CH^{Ar}$), 7.04 (m, 2H, $2CH^{Ar}$), 3.90 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 181.3 (C=O), 161.4 ($C^{Ar\text{-}q}$-OMe), 152.1 (S-*C*=C), 138.3 ($C^{Ar\text{-}q}$), 132.4 (CH^{Ar}), 132.2 (S-C=*C*), 131.8 ($2CH^{Ar}$), 131.5 ($C^{Ar\text{-}q}$), 129.6 ($C^{Ar\text{-}q}$), 129.4 (CH^{Ar}), 128.2 (CH^{Ar}), 126.4 (CH^{Ar}), 122.0 (q, J_{CF} = 328.9 Hz, $2CF_3$), 114.3 ($2CH^{Ar}$), 63.5 (CTf_2), 55.9 (OCH_3), 27.6 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.4 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1723 (C=O), 1379, 1110 (O=S=O), 1215 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}F_6O_6S_3$ [*M* + H]$^+$: 560.99295; found: 560.99056.

Bis(trifluoromethylsulfonyl)thioflavone 65c-Na. From 30 mg (0.09 mmol) of alkynone **64c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65c-Na** (22 mg, 39%) as a colorless solid; mp 311–313ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.50 (d, 1H, *J* = 8.1 Hz, CH^{Ar}), 7.68 (m, 5H, $5CH^{Ar}$), 7.38 (m, 2H, $2CH^{Ar}$), 3.66 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 180.8 (C=O), 149.8 (S-*C*=C), 137.8 ($C^{Ar\text{-}q}$), 136.5 ($C^{Ar\text{-}q}$), 132.8 (S-C=*C*), 132.5 (CH^{Ar}), 132.3 ($2CH^{Ar}$), 132.2 ($2CH^{Ar}$), 131.6 ($C^{Ar\text{-}q}$), 129.4 (CH^{Ar}), 128.4 (CH^{Ar}), 126.5 (CH^{Ar}), 124.0 ($C^{Ar\text{-}q}$), 122.0 (q, J_{CF} = 328.5 Hz, $2CF_3$), 63.6 (CTf_2), 27.5 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1721 (C=O), 1378, 1108 (O=S=O), 1213 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{12}BrF_6O_5S_3$ [*M* + H]$^+$: 608.89289; found: 608.89280.

Bis(trifluoromethylsulfonyl)thioflavone 65d-Na. From 30 mg (0.11 mmol) of alkynone **64d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65d-Na** (46 mg, 74%) as a colorless solid; mp 235–237ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.53 (m, 1H, CH^{Ar}), 7.74 (m, 2H, $2CH^{Ar}$), 7.62 (m, 1H, CH^{Ar}), 7.45 (m, 2H, $2CH^{Ar}$), 7.35 (m, 2H, $2CH^{Ar}$), 3.72 (d, 1H, *J* = 14.9 Hz, C*H*H), 3.28 (d, 1H, *J* = 14.9 Hz, C*H*H), 2.19 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 181.2 (C=O), 150.7 (S-*C*=C), 138.3 ($C^{Ar\text{-}q}$), 137.1 ($C^{Ar\text{-}q}$), 136.0 ($C^{Ar\text{-}q}$), 133.0 (S-C=*C*), 132.5 (CH^{Ar}), 131.6 ($C^{Ar\text{-}q}$), 131.2 (CH^{Ar}), 130.8 (CH^{Ar}), 130.4 (CH^{Ar}), 129.4 (CH^{Ar}), 128.3 (CH^{Ar}), 126.5 (CH^{Ar}), 126.3 (CH^{Ar}), 122.0 (q, J_{CF} = 324.5 Hz, $2CF_3$), 62.9 (CTf_2), 27.9 (CH_2), 19.4 (CH_3); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.6 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1724 (C=O), 1369, 1109 (O=S=O), 1213 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}F_6O_5S_3$ [*M* + H]$^+$: 544.99803; found: 544.99988.

Bis(trifluoromethylsulfonyl)thioflavone 65e-Na. From 20 mg (0.06 mmol) of alkynone **64e**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65e-Na** (29 mg, 77%) as a colorless solid; mp 216–218ºC; ^{1}H NMR (500 MHz, CD_3CN, 25 ºC): δ = 8.59 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.88 (m, 1H, CH^{Ar}), 7.83 (d, 1H, *J* = 8.9 Hz, CH^{Ar}), 7.73 (m, 2H, $2CH^{Ar}$), 7.57 (m, 1H, CH^{Ar}), 7.45 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.38 (d, 1H, *J* = 2.4 Hz, CH^{Ar}), 7.25 (dd, 1H, *J* = 8.9, 2.5 Hz, CH^{Ar}), 3.98 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2); ^{13}C NMR (125 MHz, CD_3CN, 25 ºC): δ = 181.6 (C=O), 159.7 ($C^{Ar\text{-}q}$-OMe), 153.3 (S-*C*=C), 138.6 ($C^{Ar\text{-}q}$), 135.8 ($C^{Ar\text{-}q}$), 132.6 (CH^{Ar}), 132.5 (S-C=*C*), 132.4 ($C^{Ar\text{-}q}$), 131.4 ($C^{Ar\text{-}q}$), 130.7 (CH^{Ar}), 129.9 (CH^{Ar}), 129.6 (CH^{Ar}), 128.8 ($C^{Ar\text{-}q}$), 128.4 (CH^{Ar}), 128.2 (CH^{Ar}), 127.4 (CH^{Ar}), 126.5 (CH^{Ar}), 122.0 (q, J_{CF} = 328.5 Hz, $2CF_3$), 120.4 (CH^{Ar}), 106.8 (CH^{Ar}), 63.4 (CTf_2), 56.0 (OCH_3), 27.9 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.4 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1725 (C=O), 1378, 1109 (O=S=O), 1212 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{17}F_6O_6S_3$ [*M* + H]$^+$: 611.00860; found: 611.00999.

Bis(trifluoromethylsulfonyl)thioflavone 65f-Na. From 20 mg (0.08 mmol) of alkynone **64f**, and after flash chromatography of the residue using hexanes/ethyl acetate

(1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65f-Na** (29 mg, 67%) as a pale yellow solid; mp 227–229ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.49 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.72 (m, 2H, $2CH^{Ar}$), 7.59 (m, 3H, $3CH^{Ar}$), 7.23 (dd, 1H, *J* = 5.0, 1.3 Hz, CH^{Ar}), 3.75 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 181.2 (C=O), 146.7 (S-*C*=C), 138.1 ($C^{Ar\text{-}q}$), 137.4 ($C^{Ar\text{-}q}$), 132.9 ($C^{Ar\text{-}q}$), 132.4 (CH^{Ar}), 131.5 (S-C=*C*), 129.6 (CH^{Ar}), 129.4 (CH^{Ar}), 128.3 (CH^{Ar}), 127.9 (CH^{Ar}), 127.1 (CH^{Ar}), 126.4 (CH^{Ar}), 122.0 (q, J_{CF} = 328.2 Hz, $2CF_3$), 63.5 (CTf_2), 27.8 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1717 (C=O), 1365, 1103 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_6O_5S_4$ [*M* + H]$^+$: 536.93880; found: 536.94086.

Bis(trifluoromethylsulfonyl)thioflavone 65g-Na. From 40 mg (0.15 mmol) of alkynone **64g**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65g-Na** (50 mg, 57%) as a pale yellow solid; mp 259–261ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 8.42 (m, 1H, CH^{Ar}), 7.65 (m, 3H, $3CH^{Ar}$), 7.48 (m, 1H, CH^{Ar}), 7.29 (dd, 1H, *J* = 3.6, 1.2 Hz, CH^{Ar}), 7.10 (dd, 1H, *J* = 5.1, 3.6 Hz, CH^{Ar}), 3.87 (s, 2H, CH_2); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 181.3 (C=O), 143.7 (S-*C*=C), 138.2 ($C^{Ar\text{-}q}$), 137.7 ($C^{Ar\text{-}q}$), 134.6 (S-C=*C*), 132.4 (CH^{Ar}), 131.6 ($C^{Ar\text{-}q}$), 131.1 (CH^{Ar}), 129.7 (CH^{Ar}), 129.6 (CH^{Ar}), 128.1 (CH^{Ar}), 128.0 (CH^{Ar}), 126.2 (CH^{Ar}), 122.2 (q, J_{CF} = 328.7 Hz, $2CF_3$), 64.1 (CTf_2), 28.1 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –79.9 (s, 6F, $2CF_3$); IR (acetone): ν = 1723 (C=O), 1359, 1102 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_6O_5S_4$ [*M* + H]$^+$: 536.93880; found: 536.93706.

Bis(trifluoromethylsulfonyl)thioflavone 65h-Na. From 30 mg (0.1 mmol) of alkynone **64h**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65h-Na** (38 mg, 64%) as a colorless solid; mp 193–195ºC; ^{1}H NMR (500 MHz, CD_3CN, 25 ºC): δ = 8.56 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.71 (m, 2H, $2CH^{Ar}$), 7.56 (m, 3H, $3CH^{Ar}$), 7.45 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.34 (m, 1H, CH^{Ar}), 7.18 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 3.92 (s, 3H, NCH_3), 3.83 (s, 2H, CH_2); ^{13}C NMR (125 MHz, CD_3CN, 25 ºC): δ = 181.5 (C=O), 146.2 (S-*C*=C), 139.1 ($C^{Ar\text{-}q}$), 137.5 ($C^{Ar\text{-}q}$), 132.7 (S-C=*C*), 132.2 (CH^{Ar}), 131.8 (CH^{Ar}), 131.7 ($C^{Ar\text{-}q}$), 129.5 (CH^{Ar}), 128.1 (CH^{Ar}), 127.4 ($C^{Ar\text{-}q}$), 126.3 (CH^{Ar}), 123.2 (CH^{Ar}), 122.0 (q, J_{CF} = 328.6 Hz, $2CF_3$), 121.3 (CH^{Ar}), 120.3 (CH^{Ar}), 111.9 ($C^{Ar\text{-}q}$), 111.1 (CH^{Ar}), 63.8 (CTf_2), 33.5 (NCH_3), 28.4 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1712 (C=O), 1361, 1104 (O=S=O), 1212 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{15}F_6NNaO_5S_3$ [*M* + Na]$^+$: 605.99088; found: 605.99322.

Bis(trifluoromethylsulfonyl)thioflavone 65i-Na. From 30 mg (0.08 mmol) of alkynone **64i**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65i-Na** (21 mg, 39%) as an orange solid; mp 206–208ºC; ^{1}H NMR (500 MHz, acetone-d_6, 25 ºC): δ = 8.35 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.69 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.62 (t, 1H, *J* = 7.0 Hz, CH^{Ar}), 7.41 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 4.68 (s, 2H, 2CH-*Cp*), 4.43 (s, 2H, 2CH-*Cp*), 4.31 (s, 5H, 5CH-*Cp*), 3.81 (s, 2H, CH_2); ^{13}C NMR (125 MHz, acetone-d_6, 25 ºC): δ = 181.2 (C=O), 138.9 ($C^{Ar\text{-}q}$), 134.1 (S-*C*=C), 132.2 (CH^{Ar}), 131.5 ($C^{Ar\text{-}q}$), 129.5 (CH^{Ar}), 127.6 (CH^{Ar}), 126.3 (CH^{Ar}), 122.3 (q, J_{CF} = 329.1 Hz, $2CF_3$), 84.6 (CTf_2), 73.1 (2CH-*Cp*), 71.7 (5CH-*Cp*), 70.3 (2CH-*Cp*), 64.0 (C^{Cq}-*Cp*), 28.2 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –79.9 (s, 6F, $2CF_3$); IR (acetone): ν = 1711 (C=O), 1358, 1107 (O=S=O), 1213 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{17}F_6FeO_5S_3$ [*M* + H]$^+$: 638.94866; found: 638.94781.

Bis(trifluoromethylsulfonyl)thioflavone 65m-Na. From 20 mg (0.07 mmol) of alkynone **64m**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound

65m-Na (29 mg, 71%) as a colorless solid; mp 256–258ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.84 (dd, 1H, *J* = 4.5, 1.8 Hz, CH^{Ar}), 8.74 (dd, 1H, *J* = 8.1, 1.8 Hz, CH^{Ar}), 7.59 (dd, 1H, *J* = 8.1, 4.5 Hz, CH^{Ar}), 7.41 (m, 2H, $2CH^{Ar}$), 7.07 (m, 2H, $2CH^{Ar}$), 3.91 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 181.9 (C=O), 161.5 ($C^{Ar\text{-}q}$), 158.6 ($C^{Ar\text{-}q}$), 153.7 (CH^{Ar}), 152.3 (S-*C*=C), 137.6 (CH^{Ar}), 132.9 (S-C=*C*), 131.8 ($2CH^{Ar}$), 129.4 ($C^{Ar\text{-}q}$), 128.6 ($C^{Ar\text{-}q}$), 123.7 (CH^{Ar}), 122.0 (q, J_{CF} = 329.0 Hz, $2CF_3$), 114.4 ($2CH^{Ar}$), 63.5 (CTf_2), 56.0 (OCH_3), 27.6 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); ^{23}Na NMR (132 MHz, CD_3CN, 25 ºC): δ = –7.0 (s, 1Na, Na^+); IR (CH_3CN): ν = 1712 (C=O), 1371, 1102 (O=S=O), 1201 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_6NO_6S_3$ [*M* + H]$^+$: 561.98819; found: 561.98819.

Bis(trifluoromethylsulfonyl)thioflavone 65n-Na. From 30 mg (0.1 mmol) of alkynone **64n**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65n-Na** (39 mg, 66%) as a colorless solid; mp 169–171ºC; ^{1}H NMR (700 MHz, CD_3CN, 25 ºC): δ = 7.25 (m, 2H, $2CH^{Ar}$), 7.01 (m, 2H, $2CH^{Ar}$), 3.88 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 2.65 (m, 2H, CH_2), 1.82 (s, 4H, $2CH_2$); ^{13}C NMR (175 MHz, CD_3CN, 25 ºC): δ = 182.2 (C=O), 161.5 ($C^{Ar\text{-}q}$-OMe), 153.8 ($C^{Ar\text{-}q}$), 151.0 (S-*C*=C), 136.1 ($C^{Ar\text{-}q}$), 134.2 (S-C=*C*), 131.9 ($2CH^{Ar}$), 128.7 ($C^{Ar\text{-}q}$), 121.8 (q, J_{CF} = 328.3 Hz, $2CF_3$), 114.4 ($2CH^{Ar}$), 62.8 (CTf_2), 55.9 (OCH_3), 30.5 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 22.5 (CH_2), 22.4 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.7 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1709 (C=O), 1362, 1107 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{19}F_6O_6S_3$ [*M* + H]$^+$: 565.02425; found: 565.02633.

Bis(trifluoromethylsulfonyl)thioflavone 65o-Na. From 30 mg (0.09 mmol) of alkynone **64o**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65o-Na** (32 mg, 56%) as a colorless solid; mp 201–203ºC; ^{1}H NMR (700 MHz, CD_3CN, 25 ºC): δ = 7.87 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.62 (m, 2H, $2CH^{Ar}$), 7.34 (m, 1H, CH^{Ar}), 7.26 (m, 2H, $2CH^{Ar}$), 6.93 (m, 2H, $2CH^{Ar}$), 4.37 (s, 3H, OCH_3), 3.88 (s, 3H, NCH_3), 3.72 (s, 2H, CH_2); ^{13}C NMR (175 MHz, CD_3CN, 25 ºC): δ = 175.1 (C=O), 161.2 ($C^{Ar\text{-}q}$-OMe), 148.5 (S-*C*=C), 140.4 ($C^{Ar\text{-}q}$), 135.3 (S-C=*C*), 131.1 ($2CH^{Ar}$), 131.5 ($C^{Ar\text{-}q}$), 130.0 ($C^{Ar\text{-}q}$), 128.4 (CH^{Ar}), 122.8 ($C^{Ar\text{-}q}$), 122.0 (q, J_{CF} = 328.7 Hz, $2CF_3$), 121.6 (CH^{Ar}), 120.9 (CH^{Ar}), 114.1 ($2CH^{Ar}$), 111.8 (CH^{Ar}), 63.6 (CTf_2), 55.9 (OCH_3), 32.7 (NCH_3), 28.1 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.2 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1721 (C=O), 1355, 1106 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{18}F_6NO_6S_3$ [*M* + H]$^+$: 614.01950; found: 614.02293.

Bis(trifluoromethylsulfonyl)thioflavone 65p-Na. From 30 mg (0.1 mmol) of alkynone **64p**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65p-Na** (38 mg, 61%) as a colorless solid; mp 250–252ºC; ^{1}H NMR (500 MHz, CD_3CN, 25 ºC): δ = 8.03 (d, 1H, *J* = 5.3 Hz, CH^{Ar}), 7.45 (d, 1H, *J* = 5.3 Hz, CH^{Ar}), 7.31 (m, 2H, $2CH^{Ar}$), 7.04 (m, 2H, $2CH^{Ar}$), 3.90 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2); ^{13}C NMR (125 MHz, CD_3CN, 25 ºC): δ = 177.3 (C=O), 161.6 ($C^{Ar\text{-}q}$-OMe), 152.8 ($C^{Ar\text{-}q}$), 140.4 (S-*C*=C), 137.8 ($C^{Ar\text{-}q}$), 135.3 (CH^{Ar}), 132.2 (S-C=*C*), 132.1 ($2CH^{Ar}$), 129.4 ($C^{Ar\text{-}q}$), 126.0 (CH^{Ar}), 122.0 (q, J_{CF} = 328.4 Hz, $2CF_3$), 114.4 ($2CH^{Ar}$), 63.4 (CTf_2), 56.0 (OCH_3), 27.6 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.5 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1701 (C=O), 1361, 1105 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{13}F_6O_6S_4$ [*M* + H]$^+$: 566.94937; found: 566.95013.

Bis(trifluoromethylsulfonyl)thioflavone 65q-Na. From 30 mg (0.11 mmol) of alkynone **64q**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **65q-Na** (27 mg, 40%) as a colorless solid; mp 279–281ºC; ^{1}H NMR (700 MHz, CD_3CN, 25 ºC): δ = 7.98 (d, 1H, *J* = 5.3 Hz, CH^{Ar}), 7.50 (m, 3H, $3CH^{Ar}$), 7.43 (m, 2H, $2CH^{Ar}$), 7.40 (d, 1H,

J = 5.3 Hz, CH^{Ar}), 3.67 (s, 2H, CH_2); ^{13}C NMR (175 MHz, CD_3CN, 25 ºC): δ = 176.7 (C=O), 150.9 ($C^{Ar\text{-}q}$), 139.2 (S-*C*=C), 137.9 ($C^{Ar\text{-}q}$), 137.4 ($C^{Ar\text{-}q}$), 134.5 (CH^{Ar}), 132.6 (S-C=*C*), 130.6 ($2CH^{Ar}$), 130.2 (CH^{Ar}), 129.0 ($2CH^{Ar}$), 126.0 (CH^{Ar}), 122.1 (q, J_{CF} = 328.7 Hz, $2CF_3$), 63.6 (CTf_2), 27.5 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.1 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1709 (C=O), 1359, 1107 (O=S=O), 1212 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_6O_5S_4$ $[M + H]^+$: 536.93880; found: 536.93889.

Bis(trifluoromethylsulfonyl)selenoflavone 67a-Na. From 30 mg (0.09 mmol) of alkynone **66a**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **67a-Na** (34 mg, 60%) as a colorless solid; mp 178–180ºC; ^1H NMR (500 MHz, CD_3CN, 25 ºC): δ = 8.54 (dd, 1H, J = 8.1, 1.1 Hz, CH^{Ar}), 7.78 (d, 1H, J = 7.9 Hz, CH^{Ar}), 7.65 (m, 1H, CH^{Ar}), 7.56 (m, 1H, CH^{Ar}), 7.32 (m, 2H, $2CH^{Ar}$), 7.03 (m, 2H, $2CH^{Ar}$), 3.90 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2); ^{13}C NMR (125 MHz, CD_3CN, 25 ºC): δ = 183.4 (C=O), 161.2 ($C^{Ar\text{-}q}$-OMe), 152.7 (S-*C*=C), 137.6 ($C^{Ar\text{-}q}$), 134.0 (S-C=*C*), 133.1 ($C^{Ar\text{-}q}$), 132.3 (CH^{Ar}), 131.3 ($2CH^{Ar}$), 131.2 (CH^{Ar}), 128.4 (CH^{Ar}), 128.3 (CH^{Ar}), 122.0 (q, J_{CF} = 328.7 Hz, $2CF_3$), 114.3 ($2CH^{Ar}$), 63.7 (CTf_2), 56.0 (OCH_3), 28.1 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); ^{77}Se-NMR (95 MHz, CD_3CN, 25 ºC) δ: 403.7 (s, 1Se, Se); IR (CH_3CN): ν = 1716 (C=O), 1377, 1109 (O=S=O), 1213 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{14}F_6NaO_6S_2Se$ $[M + Na]^+$: 630.91933; found: 630.91980.

Bis(trifluoromethylsulfonyl)selenoflavone 67b-Na. From 30 mg (0.079 mmol) of alkynone **66b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **67b-Na** (35 mg, 65%) as a colorless solid; mp 196–198ºC; ^1H NMR (500 MHz, acetone-d_6, 25 ºC): δ = 8.50 (dd, 1H, J = 8.1, 1.3 Hz, CH^{Ar}), 7.86 (s, 1H, CH^{Ar}), 7.81 (m, 2H, $2CH^{Ar}$), 7.76 (d, 1H, J = 7.9 Hz, CH^{Ar}), 7.57 (m, 1H, CH^{Ar}), 7.46 (m, 2H, $2CH^{Ar}$), 7.31 (d, 1H, J = 2.4 Hz, CH^{Ar}), 7.16 (dd, 1H, J = 8.9, 2.6 Hz, CH^{Ar}), 3.90 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2); ^{13}C NMR (125 MHz, acetone-d_6, 25 ºC): δ = 183.5 (C=O), 159.7 ($C^{Ar\text{-}q}$-OMe), 151.8 (S-*C*=C), 137.7 ($C^{Ar\text{-}q}$), 135.8 ($C^{Ar\text{-}q}$), 135.0 (S-C=*C*), 134.5 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 132.2 (CH^{Ar}), 131.5 (CH^{Ar}), 130.9 (CH^{Ar}), 129.2 ($C^{Ar\text{-}q}$), 129.2 (CH^{Ar}), 128.5 (CH^{Ar}), 128.1 ($2CH^{Ar}$), 127.5 (CH^{Ar}), 122.4 (q, J_{CF} = 329.7 Hz, $2CF_3$), 120.4 (CH^{Ar}), 106.8 (CH^{Ar}), 64.2 (CTf_2), 55.9 (OCH_3), 28.8 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –79.8 (s, 6F, $2CF_3$); ^{77}Se-NMR (95 MHz, $CDCl_3$, 25 ºC) δ: 400.3 (s, 1Se, Se); IR (acetone): ν = 1726 (C=O), 1371, 1110 (O=S=O), 1211 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{17}F_6O_6S_2Se$ $[M + H]^+$: 658.95308; found: 658.95286.

Bis(trifluoromethylsulfonyl)selenoflavone 67c-Na. From 30 mg (0.1 mmol) of alkynone **66c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **67c-Na** (33 mg, 55%) as a colorless solid; mp 194–196ºC; ^1H NMR (500 MHz, acetone-d_6, 25 ºC): δ = 8.43 (dd, 1H, J = 8.1, 1.2 Hz, CH^{Ar}), 7.73 (dd, 1H, J = 7.9, 0.7 Hz, CH^{Ar}), 7.63 (dd, 1H, J = 5.1, 1.2 Hz, CH^{Ar}), 7.56 (m, 1H, CH^{Ar}), 7.46 (m, 1H, CH^{Ar}), 7.27 (dd, 1H, J = 3.6, 1.2 Hz, CH^{Ar}), 7.10 (dd, 1H, J = 5.1, 3.6 Hz, CH^{Ar}), 3.92 (s, 2H, CH_2); ^{13}C NMR (125 MHz, acetone-d_6, 25 ºC): δ = 183.6 (C=O), 142.8 (S-*C*=C), 139.6 ($C^{Ar\text{-}q}$), 137.4 ($C^{Ar\text{-}q}$), 136.5 (S-C=*C*), 133.3 ($C^{Ar\text{-}q}$), 132.3 (CH^{Ar}), 131.4 (CH^{Ar}), 130.3 (CH^{Ar}), 129.4 (CH^{Ar}), 128.3 ($2CH^{Ar}$), 128.2 (CH^{Ar}), 122.3 (q, J_{CF} = 329.4 Hz, $2CF_3$), 64.3 (CTf_2), 28.7 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –79.8 (s, 6F, $2CF_3$); ^{77}Se-NMR (95 MHz, acetone-d_6, 25 ºC) δ: 412.9 (s, 1Se, Se); ^{23}Na NMR (132 MHz, acetone-d_6, 25 ºC): δ = –7.7 (s, 1Na, Na^+); IR (acetone): ν = 1719 (C=O), 1361, 1103 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_6O_5S_3Se$ $[M + H]^+$: 584.88315; found: 584.88568.

Bis(trifluoromethylsulfonyl)flavone 69a-Na. From 30 mg (0.13 mmol) of alkynone **68a**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as

eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **69a-Na** (43 mg, 61%) as a colorless solid; mp 202–204ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.23 (dd, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 7.81 (m, 1H, CH^{Ar}), 7.53 (m, 7H, $7CH^{Ar}$), 3.66 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 179.5 (C=O), 164.9 (O-*C*=C), 156.8 ($C^{Ar\text{-}q}$-O), 134.8 (CH^{Ar}), 134.3 ($C^{Ar\text{-}q}$), 131.0 (CH^{Ar}), 130.4 ($2CH^{Ar}$), 128.9 ($2CH^{Ar}$), 126.1 (CH^{Ar}), 125.8 (CH^{Ar}), 123.7 (O-C=*C*), 122.0 (q, J_{CF} = 327.4 Hz, $2CF_3$), 119.8 ($C^{Ar\text{-}q}$), 118.9 (CH^{Ar}), 63.4 (CTf_2), 25.4 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.5 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1731 (C=O), 1379, 1109 (O=S=O), 1205 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{12}F_6NaO_6S_2$ [*M* + Na]$^+$: 536.98717; found: 536.98816.

Bis(trifluoromethylsulfonyl)flavone 69b-Na. From 20 mg (0.08 mmol) of alkynone **68b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **69b-Na** (36 mg, 79%) as a colorless solid; mp 223–225ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.22 (dd, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 7.57 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.46 (m, 3H, $3CH^{Ar}$), 7.06 (m, 2H, $2CH^{Ar}$), 3.91 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 179.7 (C=O), 165.2 (O-*C*=C), 162.0 ($C^{Ar\text{-}q}$-OMe), 156.8 ($C^{Ar\text{-}q}$-O), 134.7 (CH^{Ar}), 132.0 ($2CH^{Ar}$), 126.5 ($C^{Ar\text{-}q}$), 126.1 (CH^{Ar}), 125.7 (CH^{Ar}), 123.6 ($C^{Ar\text{-}q}$), 121.9 (q, J_{CF} = 328.3 Hz, $2CF_3$), 119.4 (O-C=*C*), 118.8 (CH^{Ar}), 114.2 ($2CH^{Ar}$), 63.4 (CTf_2), 56.0 (OCH_3), 25.4 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.5 (s, 6F, $2CF_3$); ^{23}Na NMR (132 MHz, CD_3CN, 25 ºC): δ = –6.8 (s, 1Na, Na^+); IR (CH_3CN): ν = 1719 (C=O), 1376, 1109 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}F_6O_7S_2$ [*M* + H]$^+$: 545.01579; found: 545.01488.

Bis(trifluoromethylsulfonyl)flavone 69c-Na. From 30 mg (0.12 mmol) of alkynone **68c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **69c-Na** (53 mg, 78%) as a colorless solid; mp 178–180ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 8.14 (dd, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 7.70 (m, 1H, CH^{Ar}), 7.40 (m, 4H, $4CH^{Ar}$), 7.08 (d, 1H, *J* = 8.1 Hz, CH^{Ar}), 7.02 (m, 1H, CH^{Ar}), 3.75 (s, 3H, OCH_3), 3.45 (s, 2H, CH_2); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 179.4 (C=O), 162.2 (O-*C*=C), 158.1 ($C^{Ar\text{-}q}$-O), 157.2 ($C^{Ar\text{-}q}$-OMe), 134.4 (CH^{Ar}), 132.5 (CH^{Ar}), 132.2 (CH^{Ar}), 126.3 (CH^{Ar}), 125.4 (CH^{Ar}), 124.2 ($C^{Ar\text{-}q}$), 123.3 ($C^{Ar\text{-}q}$), 122.2 (q, J_{CF} = 329.2 Hz, $2CF_3$), 122.3 (O-C=*C*), 120.8 (CH^{Ar}), 118.8 (CH^{Ar}), 112.1 (CH^{Ar}), 63.5 (CTf_2), 56.0 (OCH_3), 26.0 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –80.1 (s, 6F, $2CF_3$); IR (acetone): ν = 1716 (C=O), 1369, 1108 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{20}H_{15}F_6O_7S_2$ [*M* + H]$^+$: 545.01579; found: 545.01402.

Bis(trifluoromethylsulfonyl)flavone 69d-Na. From 20 mg (0.07 mmol) of alkynone **68d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **69d-Na** (35 mg, 81%) as a colorless solid; mp 319–321ºC; ^{1}H NMR (500 MHz, CD_3CN, 25 ºC): δ = 8.23 (dd, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 8.05 (s, 1H, CH^{Ar}), 7.93 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 7.87 (d, 1H, *J* = 9.0 Hz, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 7.67 (dd, 1H, *J* = 8.5, 1.7 Hz, CH^{Ar}), 7.59 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 7.48 (m, 1H, CH^{Ar}), 7.40 (m, 1H, CH^{Ar}), 7.26 (dd, 1H, *J* = 8.9, 2.5 Hz, CH^{Ar}), 4.00 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2); ^{13}C NMR (125 MHz, CD_3CN, 25 ºC): δ = 179.4 (C=O), 164.9 (O-*C*=C), 159.8 ($C^{Ar\text{-}q}$-OMe), 156.8 ($C^{Ar\text{-}q}$-O), 136.2 ($C^{Ar\text{-}q}$), 134.7 (CH^{Ar}), 130.9 (CH^{Ar}), 130.4 (CH^{Ar}), 129.5 ($C^{Ar\text{-}q}$), 128.6 ($C^{Ar\text{-}q}$), 127.7 (CH^{Ar}), 127.3 (CH^{Ar}), 126.2 (CH^{Ar}), 125.7 (CH^{Ar}), 123.8 ($C^{Ar\text{-}q}$), 122.1 (q, J_{CF} = 328.6 Hz, $2CF_3$), 120.3 (CH^{Ar}), 120.1 (O-C=*C*), 118.8 (CH^{Ar}), 106.8 (CH^{Ar}), 63.7 (CTf_2), 56.0 (OCH_3), 25.4 (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.3 (s, 6F, $2CF_3$); IR (CH_3CN): ν = 1726 (C=O), 1365, 1107 (O=S=O), 1211 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{17}F_6O_7S_2$ [*M* + H]$^+$: 595.03144; found: 595.03232.

Bis(trifluoromethylsulfonyl)flavone 69e-Na. From 30 mg (0.13 mmol) of alkynone **68e**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et_2O and precipitation with hexanes) gave compound **69e-Na** (59 mg, 84%) as a colorless solid; mp 301–303ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 8.09 (dd, 1H, *J* = 8.0, 1.3 Hz, CH^{Ar}), 7.71 (m, 3H, $3CH^{Ar}$), 7.48 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.35 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.14 (dd, 1H, *J* = 5.0, 3.8 Hz, CH^{Ar}), 3.86 (s, 2H, CH_2); ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 179.0 (C=O), 157.9 (O-*C*=C), 156.3 ($C^{Ar\text{-}q}$-O), 135.4 ($C^{Ar\text{-}q}$), 134.5 (CH^{Ar}), 132.1 (CH^{Ar}), 130.5 (CH^{Ar}), 127.9 (CH^{Ar}), 126.2 (CH^{Ar}), 125.4 (CH^{Ar}), 123.4 (O-C=*C*), 122.1 (q, J_{CF} = 329.1 Hz, $2CF_3$), 119.9 ($C^{Ar\text{-}q}$), 118.4 (CH^{Ar}), 63.4 (CTf_2), 25.4 (CH_2); ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –80.0 (s, 6F, $2CF_3$); IR (acetone): ν = 1712 (C=O), 1362, 1109 (O=S=O), 1208 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_6O_6S_3$ [*M* + H]$^+$: 520.96165; found: 520.95920.

General procedure for the reaction between alkynones 64a–i, 64n–s, and 66a–c with pyridinium salt 1d at 110ºC. Preparation of triflyl-benzothienopyrans 71a–i, 71n–s, and triflyl-benzoselenophenopyrans 73a–c. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1** (0.2 mmol) was added to a hot solution (110ºC) of the appropriate alkynone **64a–i**, **64n–s**, and **66a–c** (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110ºC until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Adducts **64p** and **64q** required an extra heating in acetonitrile in sealed tube at 110ºC because after the initial heating in toluene, cyclobutenes **72p** and **72q** were isolated. Chromatography of the residue eluting with hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **71a–i**, **71n–s**, and **55a–c** follow.

Triflyl-benzothienopyran 71a. From 20 mg (0.08 mmol) of alkynone **64a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **71a** (17 mg, 53%) as a yellow solid; mp 157–159ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.89 (m, 1H, CH^{Ar}), 7.70 (m, 1H, CH^{Ar}), 7.49 (m, 5H, $5CH^{Ar}$), 7.36 (m, 2H, $2CH^{Ar}$), 5.39 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 155.2 ($C^{Ar\text{-}q}$), 154.8 ($C^{Ar\text{-}q}$), 142.2 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 129.9 (CH^{Ar}), 129.0 (CH^{Ar}), 128.4 ($C^{Ar\text{-}q}$), 128.3 ($2CH^{Ar}$), 127.9 ($2CH^{Ar}$), 125.3 (CH^{Ar}), 123.3 (CH^{Ar}), 122.9 (CH^{Ar}), 119.9 (q, J_{CF} = 326.7 Hz, CF_3), 119.6 (*C*=C-Tf), 105.8 (C=*C*-Tf), 67.2 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.0 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1382, 1111 (O=S=O), 1213 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{12}F_3O_3S_2$ [*M* + H]$^+$: 397.01745; found: 397.01904. CCDC 1528521 contains the supplementary crystallographic data for compound **71a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Triflyl-benzothienopyran 71b. From 40 mg (0.14 mmol) of alkynone **64b**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71b** (49 mg, 82%) as a yellow solid; mp 155–157ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.89 (m, 1H, CH^{Ar}), 7.71 (m, 1H, CH^{Ar}), 7.47 (m, 2H, $2CH^{Ar}$), 7.33 (m, 2H, $2CH^{Ar}$), 6.98 (m, 2H, $2CH^{Ar}$), 5.37 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 161.0 ($C^{Ar\text{-}q}$-OMe), 155.3 ($C^{Ar\text{-}q}$), 154.9 ($C^{Ar\text{-}q}$), 142.2 ($C^{Ar\text{-}q}$), 130.4 ($2CH^{Ar}$), 128.9 (CH^{Ar}), 128.5 ($C^{Ar\text{-}q}$), 125.5 ($C^{Ar\text{-}q}$), 125.2 (CH^{Ar}), 123.3 (CH^{Ar}), 122.9 (CH^{Ar}), 120.0 (q, J_{CF} = 326.8 Hz, CF_3), 119.9 (*C*=C-Tf), 113.2 (CH^{Ar}), 105.0 (C=*C*-Tf), 67.4 (OCH_2), 55.3 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.0 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1379, 1110 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_3O_4S_2$ [*M* + H]$^+$: 427.02801; found: 427.02737.

Triflyl-benzothienopyran 71c. From 30 mg (0.09 mmol) of alkynone **64c**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave

compound **71c** (24 mg, 56%) as a yellow solid; mp 152–154ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.90 (d, 1H, *J* = 7.3 Hz, CH^{Ar}), 7.71 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.61 (m, 2H, $2CH^{Ar}$), 7.49 (m, 2H, $2CH^{Ar}$), 7.24 (m, 2H, $2CH^{Ar}$), 5.37 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 155.1 ($C^{Ar\text{-}q}$), 154.0 ($C^{Ar\text{-}q}$), 142.2 ($C^{Ar\text{-}q}$), 132.4 ($C^{Ar\text{-}q}$), 131.2 ($2CH^{Ar}$), 130.0 ($2CH^{Ar}$), 129.2 (CH^{Ar}), 128.3 ($C^{Ar\text{-}q}$), 125.4 (CH^{Ar}), 124.5 ($C^{Ar\text{-}q}$), 123.3 (CH^{Ar}), 123.0 (CH^{Ar}), 119.9 (q, J_{CF} = 326.7 Hz, CF_3), 119.0 (*C*=C-Tf), 105.8 (C=*C*-Tf), 67.2 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.0 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1369, 1109 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{11}BrF_3O_3S_2$ [*M* + H]$^+$: 474.92796; found: 474.92430.

Triflyl-benzothienopyran 71d. From 30 mg (0.11 mmol) of alkynone **64d**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71d** (34 mg, 75%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.90 (m, 1H, CH^{Ar}), 7.68 (m, 1H, CH^{Ar}), 7.47 (m, 2H, $2CH^{Ar}$), 7.40 (m, 1H, CH^{Ar}), 7.30 (m, 2H, $2CH^{Ar}$), 7.18 (d, 1H, *J* = 7.5 Hz, CH^{Ar}), 5.47 (d, 1H, *J* = 12.8 Hz, OC*H*H), 5.34 (d, 1H, *J* = 12.8 Hz, OCH*H*), 2.22 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 154.9 ($C^{Ar\text{-}q}$), 154.5 ($C^{Ar\text{-}q}$), 142.1 ($C^{Ar\text{-}q}$), 135.3 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 130.0 (CH^{Ar}), 129.6 (CH^{Ar}), 128.9 (CH^{Ar}), 128.5 ($C^{Ar\text{-}q}$), 127.4 (CH^{Ar}), 125.3 (CH^{Ar}), 125.2 (CH^{Ar}), 123.4 (CH^{Ar}), 122.9 (CH^{Ar}), 119.9 (q, J_{CF} = 326.6 Hz, CF_3), 119.3 (*C*=C-Tf), 106.6 (C=*C*-Tf), 67.1 (OCH_2), 19.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1381, 1109 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_3O_3S_2$ [*M* + H]$^+$: 411.03310; found: 411.03256.

Triflyl-benzothienopyran 71e. From 20 mg (0.06 mmol) of alkynone **64e**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71e** (19 mg, 67%) as a yellow solid; mp 177–179ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.91 (d, 1H, *J* = 7.4 Hz, CH^{Ar}), 7.80 (m, 3H, $3CH^{Ar}$), 7.68 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.46 (m, 3H, $3CH^{Ar}$), 7.22 (m, 2H, $2CH^{Ar}$), 5.45 (d, 1H, *J* = 12.7 Hz, OC*H*H), 5.40 (d, 1H, *J* = 12.6 Hz, OCH*H*), 3.96 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 158.8 ($C^{Ar\text{-}q}$-OMe), 155.5 ($C^{Ar\text{-}q}$), 154.9 ($C^{Ar\text{-}q}$), 142.3 ($C^{Ar\text{-}q}$), 135.1 ($C^{Ar\text{-}q}$), 130.0 (CH^{Ar}), 128.9 (CH^{Ar}), 128.7 ($C^{Ar\text{-}q}$), 128.5 ($C^{Ar\text{-}q}$), 128.4 (CH^{Ar}), 127.7 ($C^{Ar\text{-}q}$), 126.4 (CH^{Ar}), 126.3 (CH^{Ar}), 125.2 (CH^{Ar}), 123.3 (CH^{Ar}), 123.0 (CH^{Ar}), 120.0 (q, J_{CF} = 326.8 Hz, CF_3), 119.9 (*C*=C-Tf), 119.7 (CH^{Ar}), 105.8 (CH^{Ar}), 105.6 (C=*C*-Tf), 67.4 (OCH_2), 55.4 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1379, 1108 (O=S=O), 1205 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{16}F_3O_4S_2$ [*M* + H]$^+$: 477.04366; found: 477.04152.

Triflyl-benzothienopyran 71f. From 20 mg (0.08 mmol) of alkynone **64f**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71f** (20 mg, 64%) as a yellow solid; mp 143–145ºC; ^{1}H NMR (700 MHz, $CDCl_3$, 25 ºC): δ = 7.89 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.73 (d, 1H, *J* = 8.1 Hz, CH^{Ar}), 7.55 (m, 1H, CH^{Ar}), 7.51 (m, 1H, CH^{Ar}), 7.45 (m, 1H, CH^{Ar}), 7.42 (dd, 1H, *J* = 4.9, 3.0 Hz, CH^{Ar}), 7.19 (dd, 1H, *J* = 4.8, 0.8 Hz, CH^{Ar}), 5.37 (s, 2H, OCH_2); ^{13}C NMR (175 MHz, $CDCl_3$, 25 ºC): δ = 155.0 ($C^{Ar\text{-}q}$), 150.5 ($C^{Ar\text{-}q}$), 142.0 ($C^{Ar\text{-}q}$), 132.7 ($C^{Ar\text{-}q}$), 129.0 (CH^{Ar}), 128.6 (CH^{Ar}), 128.5 ($C^{Ar\text{-}q}$), 127.8 (CH^{Ar}), 125.4 (CH^{Ar}), 125.3 (CH^{Ar}), 123.3 (CH^{Ar}), 122.9 (CH^{Ar}), 120.0 (q, J_{CF} = 326.8 Hz, CF_3), 119.3 (*C*=C-Tf), 105.7 (C=*C*-Tf), 67.3 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1365, 1111 (O=S=O), 1202 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}F_3O_3S_3$ [*M* + H]$^+$: 402.97387; found: 402.97545.

Triflyl-benzothienopyran 71g. From 40 mg (0.15 mmol) of alkynone **64g**, and after flash chromatography of the residue using hexanes/toluene (1:1) as eluent gave compound **71g** (44 mg, 71%) as a yellow solid; mp 133–135ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.89 (d, 1H, *J* = 7.2 Hz, CH^{Ar}), 7.73 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.62 (dd, 1H, *J* = 5.0, 0.8 Hz, CH^{Ar}), 7.49 (m, 2H, $2CH^{Ar}$), 7.36 (d, 1H, *J* = 3.1 Hz, CH^{Ar}), 7.16 (dd, 1H, *J* = 5.0, 3.7 Hz, CH^{Ar}), 5.38 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 155.2 ($C^{Ar\text{-}q}$), 148.4 ($C^{Ar\text{-}q}$), 142.2 ($C^{Ar\text{-}q}$), 132.1 ($C^{Ar\text{-}q}$), 131.9 (CH^{Ar}), 129.5 (CH^{Ar}), 129.2 (CH^{Ar}), 128.5 ($C^{Ar\text{-}q}$), 126.9

(CH^{Ar}), 125.3 (CH^{Ar}), 123.3 (CH^{Ar}), 123.0 (CH^{Ar}), 120.1 (q, J_{CF} = 327.0 Hz, CF_3), 119.6 (*C*=C-Tf), 106.6 (C=*C*-Tf), 67.6 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –78.6 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1369, 1105 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}F_3O_3S_3$ [*M* + H]$^+$: 402.97387; found: 402.97557.

Triflyl-benzothienopyran 71h. From 30 mg (0.1 mmol) of alkynone **64h**, and after flash chromatography of the residue using hexanes/ethyl acetate (96:4) as eluent gave compound **71h** (33 mg, 76%) as an orange solid; mp 191–193ºC; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (m, 1H, CH^{Ar}), 7.56 (m, 1H, CH^{Ar}), 7.31 (m, 6H, 6CH^{Ar}), 7.03 (m, 1H, CH^{Ar}), 5.47 (d, 1H, *J* = 12.8 Hz, OC*H*H), 5.20 (d, 1H, *J* = 12.8 Hz, OCH*H*), 3.80 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 155.1 ($C^{Ar\text{-}q}$), 149.5 ($C^{Ar\text{-}q}$), 141.7 ($C^{Ar\text{-}q}$), 136.7 ($C^{Ar\text{-}q}$), 133.1 (CH^{Ar}), 128.9 ($C^{Ar\text{-}q}$), 128.7 (CH^{Ar}), 126.8 ($C^{Ar\text{-}q}$), 125.0 (CH^{Ar}), 123.3 (CH^{Ar}), 122.8 (CH^{Ar}), 122.6 (CH^{Ar}), 120.9 (CH^{Ar}), 120.5 (CH^{Ar}), 120.2 (q, J_{CF} = 327.4 Hz, CF_3), 120.0 (*C*=C-Tf), 109.8 (CH^{Ar}), 106.9 ($C^{Ar\text{-}q}$), 103.2 (C=*C*-Tf), 67.8 (OCH_2), 33.4 (NCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1372, 1103 (O=S=O), 1206 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{14}F_3NNaO_3S_2$ [*M* + Na]$^+$: 472.02594; found: 472.02708.

Triflyl-benzothienopyran 71i. From 29 mg (0.08 mmol) of alkynone **64i**, and after flash chromatography of the residue using hexanes/ethyl acetate (99:1) as eluent gave compound **71i** (9 mg, 22%; partial decomposition during chromatographic purification) as a green solid; mp 161–163ºC; ^1H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.68 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.30 (m, 1H, CH^{Ar}), 7.02 (m, 2H, 2CH^{Ar}), 5.02 (s, 2H, OCH_2), 4.92 (s, 2H, 2CH-*Cp*), 4.17 (s, 2H, 2CH-*Cp*), 4.07 (s, 5H, 5CH-*Cp*); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ = 156.6 ($C^{Ar\text{-}q}$), 141.7 ($C^{Ar\text{-}q}$), 129.3 ($C^{Ar\text{-}q}$), 129.1 (CH^{Ar}), 125.1 (CH^{Ar}), 122.8 (CH^{Ar}), 122.7 (CH^{Ar}), 121.0 (q, J_{CF} = 328.1 Hz, CF_3), 118.4 (*C*=C-Tf), 101.2 (C=*C*-Tf), 78.3 (C^{Cq}-*Cp*), 73.9 (2CH-*Cp*), 71.5 (2CH-*Cp*), 71.4 (5CH-*Cp*), 68.6 (OCH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –78.3 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1372, 1109 (O=S=O), 1208 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{16}F_3FeO_3S_2$ [*M* + H]$^+$: 504.98372; found: 504.98577.

Triflyl-benzothienopyran 71n. From 30 mg (0.1 mmol) of alkynone **64n**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71n** (32 mg, 71%) as a yellow solid; mp 119–121ºC; ^1H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.23 (m, 2H, 2CH^{Ar}), 6.71 (m, 2H, 2CH^{Ar}), 5.09 (s, 2H, OCH_2), 3.20 (s, 3H, OCH_3), 2.15 (m, 4H, 2CH_2), 1.25 (m, 4H, 2CH_2); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ = 161.3 ($C^{Ar\text{-}q}$-OMe), 159.2 ($C^{Ar\text{-}q}$), 155.4 ($C^{Ar\text{-}q}$), 150.1 ($C^{Ar\text{-}q}$), 131.1 (2CH^{Ar}), 126.4 ($C^{Ar\text{-}q}$), 126.1 ($C^{Ar\text{-}q}$), 121.1 (q, J_{CF} = 327.2 Hz, CF_3), 118.7 (*C*=C-Tf), 113.4 (2CH^{Ar}), 101.7 (C=*C*-Tf), 67.7 (OCH_2), 54.7 (OCH_3), 26.2 (CH_2), 22.8 (CH_2), 22.2 (CH_2), 21.5 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –79.4 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1355, 1108 (O=S=O), 1199 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}F_3O_4S_2$ [*M* + H]$^+$: 431.05931; found: 431.06095.

Triflyl-benzothienopyran 71o. From 30 mg (0.09 mmol) of alkynone **64o**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **71o** (23 mg, 55%) as an orange solid; mp 133–135ºC; ^1H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.42 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.32 (m, 2H, 2CH^{Ar}), 7.20 (m, 1H, CH^{Ar}), 7.00 (m, 1H, CH^{Ar}), 6.87 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 6.76 (m, 2H, 2CH^{Ar}), 5.13 (s, 2H, OCH_2), 3.22 (s, 3H, OCH_3), 3.15 (s, 3H, NCH_3); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ = 161.5 ($C^{Ar\text{-}q}$-OMe), 156.8 ($C^{Ar\text{-}q}$), 146.1 ($C^{Ar\text{-}q}$), 143.8 ($C^{Ar\text{-}q}$), 132.0 ($C^{Ar\text{-}q}$), 131.6 (2CH^{Ar}), 126.7 ($C^{Ar\text{-}q}$), 126.3 (CH^{Ar}), 126.1 ($C^{Ar\text{-}q}$), 122.7 (*C*=C-Tf), 121.7 ($C^{Ar\text{-}q}$), 121.2 (q, J_{CF} = 327.4 Hz, CF_3), 120.4 (CH^{Ar}), 120.3 (CH^{Ar}), 113.4 (2CH^{Ar}), 110.4 (CH^{Ar}), 101.2 (C=*C*-Tf), 68.1 (OCH_2), 54.7 (OCH_3), 30.3 (NCH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –79.3 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1365, 1107 (O=S=O), 1203 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{17}F_3NO_4S_2$ [*M* + H]$^+$: 480.05456; found: 480.05541.

Bis(triflyl)cyclobutene 72p. From 30 mg (0.11 mmol) of alkynone **64p**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **72p** (60 mg, 94%) as a yellow solid; mp 106–108ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 7.89 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 7.69 (m, 2H, $2CH^{Ar}$), 7.50 (m, 3H, $3CH^{Ar}$), 7.25 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 3.99 (s, 2H, CH_2), 2.64 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 179.0 (C=O), 152.3 (*C*=C), 147.8 ($C^{Ar\text{-}q}$), 138.4 ($C^{Ar\text{-}q}$), 136.8 (CH^{Ar}), 132.3 (CH^{Ar}), 129.7 ($2CH^{Ar}$), 129.5 ($2CH^{Ar}$), 129.3 (C=*C*), 128.1 ($C^{Ar\text{-}q}$), 127.8 (CH^{Ar}), 120.6 (q, J_{CF} = 330.7 Hz, $2CF_3$), 86.7 (CTf_2), 37.5 (CH_2), 16.6 (SCH_3); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –71.2 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1365, 1109 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{13}F_6O_5S_4$ [*M* + H]$^+$: 550.95445; found: 550.95475.

Triflyl-benzothienopyran 71p. From 60 mg (0.1 mmol) of cyclobutene **72p**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71p** (35 mg, 75%) as a yellow solid; mp 172–174ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.66 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 7.49 (m, 3H, $3CH^{Ar}$), 7.37 (m, 2H, $2CH^{Ar}$), 7.20 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 5.35 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 155.8 ($C^{Ar\text{-}q}$), 152.9 ($C^{Ar\text{-}q}$), 146.4 ($C^{Ar\text{-}q}$), 133.7 (CH^{Ar}), 133.5 ($C^{Ar\text{-}q}$), 129.9 (CH^{Ar}), 128.5 ($2CH^{Ar}$), 127.7 ($2CH^{Ar}$), 127.5 (*C*=C-Tf), 122.1 ($C^{Ar\text{-}q}$), 120.8 (CH^{Ar}), 120.0 (q, J_{CF} = 326.8 Hz, CF_3), 102.7 (C=*C*-Tf), 67.6 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.1 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1365, 1107 (O=S=O), 1205 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_9F_3NaO_3S_3$ [*M* + Na]$^+$: 424.95581; found: 424.95644.

Bis(triflyl)cyclobutene 72q. From 30 mg (0.1 mmol) of alkynone **64q**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **72q** (60 mg, quantitative yield) as a red solid; mp 84–86ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.90 (m, 2H, $2CH^{Ar}$), 7.64 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 7.09 (d, 1H, *J* = 5.2 Hz, CH^{Ar}), 6.90 (m, 2H, $2CH^{Ar}$), 3.84 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 2.59 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 177.9 (C=O), 162.1 ($C^{Ar\text{-}q}$-OMe), 151.4 (*C*=C), 140.8 ($C^{Ar\text{-}q}$), 140.0 ($C^{Ar\text{-}q}$), 134.1 (CH^{Ar}), 131.7 ($2CH^{Ar}$), 128.3 ($C^{Ar\text{-}q}$), 127.7 ($C^{Ar\text{-}q}$), 126.1 (CH^{Ar}), 121.2 (C=*C*), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 114.0 ($2CH^{Ar}$), 85.7 (CTf_2), 55.3 (OCH_3), 36.3 (CH_2), 16.6 (SCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.4 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1361, 1109 (O=S=O), 1206 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{15}F_6O_6S_4$ [*M* + H]$^+$: 580.96502; found: 580.96306.

Triflyl-benzothienopyran 71q. From 60 mg (0.1 mmol) of cyclobutene **72q**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71q** (38 mg, 86%) as a yellow solid; mp 151–153ºC; ^{1}H NMR (700 MHz, $CDCl_3$, 25 ºC): δ = 7.66 (d, 1H, *J* = 5.1 Hz, CH^{Ar}), 7.33 (m, 2H, $2CH^{Ar}$), 7.22 (d, 1H, *J* = 5.1 Hz, CH^{Ar}), 6.96 (m, 2H, $2CH^{Ar}$), 5.33 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (175 MHz, $CDCl_3$, 25 ºC): δ = 161.0 ($C^{Ar\text{-}q}$-OMe), 156.0 ($C^{Ar\text{-}q}$), 153.1 ($C^{Ar\text{-}q}$), 146.3 ($C^{Ar\text{-}q}$), 133.6 (CH^{Ar}), 130.7 ($2CH^{Ar}$), 127.6 ($C^{Ar\text{-}q}$), 125.3 ($C^{Ar\text{-}q}$), 122.5 (*C*=C-Tf), 120.1 (q, J_{CF} = 326.9 Hz, CF_3), 120.8 (CH^{Ar}), 113.1 ($2CH^{Ar}$), 101.8 (C=*C*-Tf), 67.7 (OCH_2), 55.3 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.2 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1366, 1110 (O=S=O), 1203 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{11}F_3NaO_4S_3$ [*M* + Na]$^+$: 454.96638; found: 454.96624.

Triflyl-benzothienopyran 71r. From 20 mg (0.05 mmol) of alkynone **64r**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71r** (17 mg, 65%) as a yellow solid; mp 202–204ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 8.18 (d, 2H, *J* = 7.7 Hz, $2CH^{Ar}$), 7.94 (d, 1H, *J* = 7.8 Hz, CH^{Ar}), 7.77 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.70 (m, 2H, $2CH^{Ar}$), 7.62 (m, 2H, $2CH^{Ar}$), 7.53 (m, 3H, $3CH^{Ar}$), 7.48 (m, 3H, $3CH^{Ar}$), 7.34 (m, 2H, $2CH^{Ar}$), 5.45 (s, 2H, OCH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 155.1 ($C^{Ar\text{-}q}$), 154.3 ($C^{Ar\text{-}q}$), 142.3 ($C^{Ar\text{-}q}$), 140.5 ($2C^{Ar\text{-}q}$), 139.3 ($C^{Ar\text{-}q}$), 132.3 ($C^{Ar\text{-}q}$), 130.2 ($2CH^{Ar}$), 129.2 (CH^{Ar}), 128.5 ($C^{Ar\text{-}q}$), 126.2 ($2CH^{Ar}$), 126.1 ($2CH^{Ar}$), 125.4 (CH^{Ar}), 123.6 ($2C^{Ar\text{-}$

^{q}), 123.4 (CH^{Ar}), 123.1 (CH^{Ar}), 120.4 ($2CH^{Ar}$), 120.3 ($2CH^{Ar}$), 120.0 (q, J_{CF} = 326.7 Hz, CF_3), 119.3 (*C*=C-Tf), 109.8 ($2CH^{Ar}$), 106.1 (C=*C*-Tf), 67.3 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1373, 1102 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{30}H_{19}F_3NO_3S_2$ [*M* + H]$^{+}$: 562.07530; found: 562.07469.

Bis(triflyl-benzothienopyran) 71s. From 30 mg (0.07 mmol) of alkynone **64s**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **71s** (31 mg, 77%) as a yellow solid; mp 201–203ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.89 (d, 1H, *J* = 7.7 Hz, $2CH^{Ar}$), 7.78 (d, 1H, *J* = 8.0 Hz, $2CH^{Ar}$), 7.49 (m, 4H, $4CH^{Ar}$), 7.33 (s, 2H, $2CH^{Ar}$), 5.40 (s, 4H, $2OCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 155.4 ($C^{Ar\text{-}q}$), 146.9 ($C^{Ar\text{-}q}$), 142.4 ($C^{Ar\text{-}q}$), 135.8 ($C^{Ar\text{-}q}$), 131.0 ($2CH^{Ar}$), 129.4 ($2CH^{Ar}$), 128.3 ($C^{Ar\text{-}q}$), 125.4 ($2CH^{Ar}$), 123.5 ($2CH^{Ar}$), 123.0 ($2CH^{Ar}$), 120.0 (q, J_{CF} = 326.6 Hz, $2CF_3$), 119.3 (*C*=C-Tf), 107.4 (C=*C*-Tf), 67.5 ($2OCH_2$); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –78.4 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1371, 1109 (O=S=O), 1211 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{28}H_{18}F_6NO_6S_5$ [*M* + NH_4]$^{+}$: 737.96364; found: 737.96295.

Triflyl-benzoselenophenopyran 73a. From 30 mg (0.09 mmol) of alkynone **66a**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **73a** (29 mg, 68%) as a yellow solid; mp 154–156ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.91 (m, 1H, CH^{Ar}), 7.79 (m, 1H, CH^{Ar}), 7.45 (m, 2H, $2CH^{Ar}$), 7.33 (m, 2H, $2CH^{Ar}$), 6.97 (m, 2H, $2CH^{Ar}$), 5.35 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ = 160.9 ($C^{Ar\text{-}q}$-OMe), 156.7 ($C^{Ar\text{-}q}$), 156.5 ($C^{Ar\text{-}q}$), 142.5 ($C^{Ar\text{-}q}$), 131.3 ($C^{Ar\text{-}q}$), 130.0 ($2CH^{Ar}$), 129.0 (CH^{Ar}), 127.2 ($C^{Ar\text{-}q}$), 126.2 (CH^{Ar}), 125.5 (CH^{Ar}), 124.9 (CH^{Ar}), 120.1 (q, J_{CF} = 326.9 Hz, CF_3), 120.0 (*C*=C-Tf), 113.2 ($2CH^{Ar}$), 105.0 (C=*C*-Tf), 67.0 (OCH_2), 55.2 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –79.0 (s, 3F, CF_3); ^{77}Se-NMR (95 MHz, $CDCl_3$, 25 ^{o}C) δ: 440.3 (s, 1Se, Se); IR ($CHCl_3$): ν = 1376, 1109 (O=S=O), 1208 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{13}F_3NaO_4SSe$ [*M* + Na]$^{+}$: 496.95444; found: 496.95371.

Triflyl-benzoselenophenopyran 73b. From 30 mg (0.079 mmol) of alkynone **66b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **73b** (39 mg, 91%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.94 (m, 1H, CH^{Ar}), 7.78 (m, 4H, $4CH^{Ar}$), 7.45 (m, 3H, $3CH^{Ar}$), 7.22 (m, 2H, $2CH^{Ar}$), 5.44 (d, 1H, *J* = 12.7 Hz, OC*H*H), 5.38 (d, 1H, *J* = 12.7 Hz, OCH*H*), 3.96 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 158.8 ($C^{Ar\text{-}q}$-OMe), 156.8 ($C^{Ar\text{-}q}$), 156.4 ($C^{Ar\text{-}q}$), 142.7 ($C^{Ar\text{-}q}$), 135.1 ($C^{Ar\text{-}q}$), 131.3 ($C^{Ar\text{-}q}$), 130.3 ($C^{Ar\text{-}q}$), 130.0 (CH^{Ar}), 129.0 (CH^{Ar}), 127.9 (CH^{Ar}), 127.7 ($C^{Ar\text{-}q}$), 126.3 (CH^{Ar}), 126.2 (CH^{Ar}), 126.1 (CH^{Ar}), 125.6 (CH^{Ar}), 125.0 (CH^{Ar}), 120.1 (q, J_{CF} = 326.9 Hz, CF_3), 119.9 (*C*=C-Tf), 119.7 (CH^{Ar}), 105.8 (CH^{Ar}), 105.6 (C=*C*-Tf), 67.0 (OCH_2), 55.4 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –78.9 (s, 3F, CF_3); ^{77}Se-NMR (95 MHz, $CDCl_3$, 25 ^{o}C) δ: 441.7 (s, 1Se, Se); IR ($CHCl_3$): ν = 1371, 1109 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{16}F_3O_4SSe$ [*M* + H]$^{+}$: 524.98819; found: 524.98730.

Triflyl-benzoselenophenopyran 73c. From 30 mg (0.1 mmol) of alkynone **66c**, and after flash chromatography of the residue using hexanes/toluene (1:1) as eluent gave compound **73c** (36 mg, 81%) as an orange solid; mp 121–123ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.91 (m, 1H, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 7.58 (d, 1H, *J* = 4.9 Hz, CH^{Ar}), 7.46 (m, 2H, $2CH^{Ar}$), 7.33 (m, 1H, CH^{Ar}), 7.14 (m, 1H, CH^{Ar}), 5.36 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ = 156.8 ($C^{Ar\text{-}q}$), 149.9 ($C^{Ar\text{-}q}$), 142.6 ($C^{Ar\text{-}q}$), 133.7 ($C^{Ar\text{-}q}$), 131.3 (CH^{Ar}), 131.2 ($C^{Ar\text{-}q}$), 129.2 (CH^{Ar}), 129.0 (CH^{Ar}), 126.9 (CH^{Ar}), 126.2 (CH^{Ar}), 125.6 (CH^{Ar}), 125.0 (CH^{Ar}), 120.1 (q, J_{CF} = 327.0 Hz, CF_3), 119.6 (*C*=C-Tf), 106.7 (C=*C*-Tf), 67.1 (OCH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ^{o}C): δ = –78.6 (s, 3F, CF_3); ^{77}Se-NMR (95 MHz, $CDCl_3$, 25 ^{o}C) δ: 446.0 (s, 1Se, Se); IR ($CHCl_3$): ν = 1370, 1107 (O=S=O), 1201 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}F_3O_3S_2Se$ [*M* + H]$^{+}$: 450.91826; found: 450.91820.

General procedure for the reaction between alkynones 68a–e and pyridinium salt 1d at 110ºC. Preparation of triflyl-allylidenebenzofuranones 76a–e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.2 mmol) was added to a hot solution (110ºC) of the appropriate alkynone **68a–e** (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110ºC until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Next, K_2CO_3 (2 equiv.) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL). The resulting mixture was heated at 110ºC (typically 15 min) in a sealed tube. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for adducts **76a–e** follow. After the first reaction step, spirocyclic cyclobutene **74d** was isolated and fully characterized.

Triflyl-allylidenebenzofuranone 76a. From 30 mg (0.13 mmol) of alkynone **68a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **76a** (31 mg, 61%) as a yellow solid; mp 128–130ºC; ^{1}H NMR (700 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 7.79 (d, 1H, *J* = 7.3 Hz, CH^{Ar}), 7.69 (m, 3H, $3CH^{Ar}$), 7.52 (m, 3H, $3CH^{Ar}$), 7.33 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.30 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 6.70 (s, 2H, $=CH_2$); ^{13}C NMR (175 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 164.7 ($C^{Ar\text{-}q}$-O), 146.0 ($C^{Ar\text{-}q}$), 137.1 (CH^{Ar}), 131.7 ($C^{Ar\text{-}q}$), 130.2 (CH^{Ar}), 129.8 ($2CH^{Ar}$), 128.7 ($2CH^{Ar}$), 124.6 (CH^{Ar}), 124.2 (CH^{Ar}), 121.3 (*C*=C), 119.8 (q, J_{CF} = 328.0 Hz, CF_3), 113.0 (CH^{Ar}), 99.6 (*C*-Tf); ^{19}F NMR (282 MHz, $Cl_2DC–CDCl_2$, 25 ºC): δ = –77.3 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1705 (C=O), 1363, 1107 (O=S=O), 1208 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{12}F_3O_4S$ [*M* + H]$^+$: 381.04029; found: 381.04178.

Triflyl-allylidenebenzofuranone 76b. From 20 mg (0.08 mmol) of alkynone **68b**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **76b** (25 mg, 78%) as a yellow solid; mp 178–180ºC; ^{1}H NMR (700 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 7.79 (d, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.70 (m, 3H, $3CH^{Ar}$), 7.35 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.29 (t, 1H, *J* = 7.4 Hz, CH^{Ar}), 7.05 (m, 2H, $2CH^{Ar}$), 6.74 (s, 2H, $=CH_2$), 3.91 (s, 3H, OCH_3); ^{13}C NMR (175 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 164.6 ($C^{Ar\text{-}q}$-O), 161.2 ($C^{Ar\text{-}q}$-OMe), 145.2 ($C^{Ar\text{-}q}$), 136.8 (CH^{Ar}), 131.9 ($2CH^{Ar}$), 124.6 ($C^{Ar\text{-}q}$), 124.1 (CH^{Ar}), 123.9 (CH^{Ar}), 121.5 (*C*=C), 119.8 (q, J_{CF} = 328.1 Hz, CF_3), 114.4 ($2CH^{Ar}$), 113.0 (CH^{Ar}), 99.6 (*C*-Tf), 55.6 (OCH_3); ^{19}F NMR (282 MHz, $Cl_2DC–CDCl_2$, 25 ºC): δ = –75.3 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1703 (C=O), 1365, 1106 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_3O_5S$ [*M* + H]$^+$: 411.05086; found: 411.05121.

Triflyl-allylidenebenzofuranone 76c. From 30 mg (0.11 mmol) of alkynone **68c**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **76c** (37 mg, 76%) as a yellow solid; mp 140–142ºC; ^{1}H NMR (700 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 7.75 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.60 (m, 1H, CH^{Ar}), 7.49 (m, 1H, CH^{Ar}), 7.29 (m, 3H, $3CH^{Ar}$), 7.08 (t, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.02 (d, 1H, *J* = 8.4 Hz, CH^{Ar}), 6.5 (s, 2H, $=CH_2$), 3.80 (s, 3H, OCH_3); ^{13}C NMR (175 MHz, $Cl_2DC–CDCl_2$, 60 ºC): δ = 182.1 (C=O), 165.1 ($C^{Ar\text{-}q}$-O), 157.5 ($C^{Ar\text{-}q}$-OMe), 147.0 ($C^{Ar\text{-}q}$), 139.8 ($=CH_2$), 137.6 (CH^{Ar}), 132.1 (CH^{Ar}), 131.4 (CH^{Ar}), 131.2 (CH^{Ar}), 124.7 ($C^{Ar\text{-}q}$), 123.9 (CH^{Ar}), 120.6 (*C*=C), 120.4 (CH^{Ar}), 119.8 (q, J_{CF} = 327.9 Hz, CF_3), 112.9 (CH^{Ar}), 111.4 (CH^{Ar}), 99.6 (*C*-Tf), 55.7 (OCH_3); ^{19}F NMR (282 MHz, $Cl_2DC–CDCl_2$, 25 ºC): δ = –77.3 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1704 (C=O), 1364, 1101 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_3O_5S$ [*M* + H]$^+$: 411.05086; found: 411.05044.

Spirocyclic (triflyl)cyclobutene 74d. From 20 mg (0.07 mmol) of alkynone **68d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **74d** (7 mg, 23%; partial decomposition during chromatographic purification) as a yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.02 (s, 1H, CH^{Ar}), 7.88 (d, 1H, *J* = 8.6 Hz,

CH^{Ar}), 7.50 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.20 (d, 1H, *J* = 7.2 Hz, CH^{Ar}), 7.04 (m, 2H, $2CH^{Ar}$), 6.84 (dd, 1H, *J* = 9.0, 2.4 Hz, CH^{Ar}), 6.75 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 6.62 (m, 1H, CH^{Ar}), 6.56 (d, 1H, *J* = 2.2 Hz, CH^{Ar}), 3.19 (s, 3H, OCH_3), 3.10 (d, 1H, *J* = 12.2 Hz, C*H*H), 3.04 (d, 1H, *J* = 12.2 Hz, CH*H*); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 195.4 (C=O), 171.2 ($C^{Ar\text{-}q}$), 161.7 (*C*=C-Tf), 160.5 ($C^{Ar\text{-}q}$-OMe), 138.6 (CH^{Ar}), 137.2 ($C^{Ar\text{-}q}$), 131.5 (CH^{Ar}), 131.4 (CH^{Ar}), 128.1 (CH^{Ar}), 125.7 (CH^{Ar}), 125.2 (CH^{Ar}), 123.4 ($C^{Ar\text{-}q}$), 123.1 (CH^{Ar}), 120.8 ($C^{Ar\text{-}q}$), 120.2 (CH^{Ar}), 113.7 (CH^{Ar}), 105.9 (CH^{Ar}), 99.8 (C=*C*-Tf), 85.5 (C^{q}-*spirocyclic*), 54.8 (OCH_3), 41.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –78.5 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1712 (C=O), 1362, 1108 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{16}F_3O_5S$ [*M* + H]$^+$: 461.06651; found: 461.06806.

Triflyl-allylidenebenzofuranone 76d. From 30 mg (0.1 mmol) of alkynone **68d**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **76d** (38 mg, 83%) as a red solid; mp 192–194ºC; ^{1}H NMR (700 MHz, Cl_2DC–$CDCl_2$, 60 ºC): δ = 8.10 (s, 1H, CH^{Ar}), 7.84 (m, 4H, $4CH^{Ar}$), 7.70 (d, 1H, *J* = 7.7 Hz, CH^{Ar}), 7.36 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.30 (d, 1H, *J* = 7.4 Hz, CH^{Ar}), 7.26 (dd, 1H, *J* = 8.8, 2.2 Hz, CH^{Ar}), 7.22 (s, 1H, CH^{Ar}), 6.80 (s, 2H, =CH_2), 3.99 (s, 3H, OCH_3); ^{13}C NMR (175 MHz, Cl_2DC–$CDCl_2$, 60 ºC): δ = 181.8 (C=O), 164.6 ($C^{Ar\text{-}q}$-O), 159.5 ($C^{Ar\text{-}q}$-OMe), 145.9 ($C^{Ar\text{-}q}$), 136.9 ($C^{Ar\text{-}q}$), 135.3 ($C^{Ar\text{-}q}$), 130.6 H^{Ar}), 130.5 (CH^{Ar}), 128.4 ($C^{Ar\text{-}q}$), 127.2 (CH^{Ar}), 127.0 (CH^{Ar}), 124.7 (CH^{Ar}), 124.1 (CH^{Ar}), 120.7 (*C*=C), 119.8 (q, J_{CF} = 328.1 Hz, CF_3), 119.7 (CH^{Ar}), 113.0 (CH^{Ar}), 106.1 (CH^{Ar}), 99.6 (*C*-Tf), 55.7 (OCH_3); ^{19}F NMR (282 MHz, Cl_2DC–$CDCl_2$, 25 ºC): δ = –76.5 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1702 (C=O), 1366, 1105 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{16}F_3O_5S$ [*M* + H]$^+$: 461.06651; found: 461.06809.

Triflyl-allylidenebenzofuranone 76e. From 30 mg (0.13 mmol) of alkynone **68e**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **76e** (34 mg, 67%) as a yellow solid; mp 170–172ºC; ^{1}H NMR (700 MHz, Cl_2DC–$CDCl_2$, 25 ºC): δ = 7.76 (m, 2H, $2CH^{Ar}$), 7.72 (m, 1H, CH^{Ar}), 7.47 (d, 1H, *J* = 3.6 Hz, CH^{Ar}), 7.41 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.28 (t, 1H, *J* = 7.4 Hz, CH^{Ar}), 7.21 (m, 2H, CH^{Ar}, =C*H*H), 6.76 (s, 1H, =CH*H*); ^{13}C NMR (175 MHz, Cl_2DC–$CDCl_2$, 25 ºC): δ = 183.1 (C=O), 165.1 ($C^{Ar\text{-}q}$-O), 146.0 ($C^{Ar\text{-}q}$), 143.6 ($C^{Ar\text{-}q}$), 141.1 (=CH_2), 139.7 (*C*=C), 137.6 (CH^{Ar}), 136.4 (C=*C*), 133.5 (CH^{Ar}), 132.4 (CH^{Ar}), 128.2 (CH^{Ar}), 125.0 (CH^{Ar}), 124.4 (CH^{Ar}), 121.9 (CH^{Ar}), 119.8 (q, J_{CF} = 327.7 Hz, CF_3), 113.2 (CH^{Ar}), 112.3 (*C*-Tf); ^{19}F NMR (282 MHz, Cl_2DC–$CDCl_2$, 25 ºC): δ = –76.2 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1694 (C=O), 1368, 1104 (O=S=O), 1208 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{10}F_3O_4S_2$ [*M* + H]$^+$: 386.99671; found: 386.99642. CCDC 1815354 contains the supplementary crystallographic data for compound **76e** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the reaction between alkynones 70a–e and pyridinium salt 1d at 110ºC. Preparation of triflyl-2,5-dihydropyrano[3,2-*b*]indoles 77a–e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.2 mmol) was added to a hot solution (110ºC) of the appropriate alkynone **70a–e** (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110ºC until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Next, K_2CO_3 (3 equiv.) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL). The resulting mixture was heated at 90ºC (typically 15 min) in a sealed tube. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for adducts **77a–e** follow. After the first reaction step, cyclobutenes **78a–c** were isolated and fully characterized.

Bis(triflyl)cyclobutene 78a. From 30 mg (0.1 mmol) of alkynone **71a**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **78a** (50 mg, 85%) as a pale yellow solid; mp 148–150ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 11.14 (s, 1H, NH), 9.05 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.86 (dd, 1H, *J* = 8.0, 1.4 Hz, CH^{Ar}), 7.64 (m, 2H, $2CH^{Ar}$), 7.03 (t, 1H, *J* = 7.9 Hz, CH^{Ar}), 6.47 (t, 1H, *J* = 7.7 Hz, CH^{Ar}), 6.32 (m, 2H, $2CH^{Ar}$), 3.40 (s, 2H, CH_2), 2.99 (s, 3H, OCH_3), 1.79 (s, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 192.3 (C=O), 168.8 (NC=O), 162.3 ($C^{Ar\text{-}q}$-OMe), 142.4 ($C^{Ar\text{-}q}$), 142.1 (*C*=C), 138.7 ($C^{Ar\text{-}q}$), 137.0 (CH^{Ar}), 132.9 (CH^{Ar}), 131.1 ($2CH^{Ar}$), 122.8 (CH^{Ar}), 121.1 (CH^{Ar}), 120.8 ($C^{Ar\text{-}q}$), 120.4 (q, J_{CF} = 331.7 Hz, $2CF_3$), 119.7 (C=*C*), 114.6 ($2CH^{Ar}$), 86.0 (CTf_2), 54.8 (OCH_3), 36.5 (CH_2), 24.8 (CH_3); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.6 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 3451 (NH), 1685, 1662 (C=O), 1367, 1111 (O=S=O), 1204 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{18}F_6NO_7S_2$ [*M* + H]$^+$: 586.04234; found: 586.04129.

Triflyl-2,5-dihydropyrano[3,2-*b*]indole 77a. From 50 mg (0.08 mmol) of alkynone **71a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **77a** (26 mg, 67%) as a yellow solid; mp 161–163ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 50 ºC): δ = 8.29 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.78 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.61 (m, 1H, CH^{Ar}), 7.39 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.26 (m, 2H, $2CH^{Ar}$), 6.94 (m, 2H, $2CH^{Ar}$), 5.31 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 1.85 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 50 ºC): δ = 168.7 (C=O), 161.8 ($C^{Ar\text{-}q}$-OMe), 155.7 ($C^{Ar\text{-}q}$), 151.2 ($C^{Ar\text{-}q}$), 141.4 ($C^{Ar\text{-}q}$), 132.7 ($2CH^{Ar}$), 131.9 (CH^{Ar}), 124.5 (CH^{Ar}), 124.3 ($C^{Ar\text{-}q}$), 122.2 (*C*=C-Tf), 120.6 (CH^{Ar}), 120.3 (q, J_{CF} = 327.2 Hz, CF_3), 117.3 ($C^{Ar\text{-}q}$), 116.6 (CH^{Ar}), 113.5 (CH^{Ar}), 99.2 (C=*C*-Tf), 69.8 (OCH_2), 55.3 (OCH_3), 26.2 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1662 (C=O), 1368, 1112 (O=S=O), 1211 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{17}F_3NO_5S$ [*M* + H]$^+$: 452.07740; found: 452.07714.

Bis(triflyl)cyclobutene 78b. From 20 mg (0.07 mmol) of alkynone **71b**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **78b** (33 mg, 80%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 10.88 (s, 1H, NH), 8.72 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 7.86 (d, 1H, *J* = 3.8 Hz, CH^{Ar}), 7.80 (d, 1H, *J* = 7.9, 1.4 Hz, CH^{Ar}), 7.63 (m, 1H, CH^{Ar}), 7.53 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 7.11 (m, 2H, $2CH^{Ar}$), 3.81 (s, 2H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 190.3 (C=O), 169.4 (NC=O), 141.1 (*C*=C), 138.3 ($C^{Ar\text{-}q}$), 136.5 (CH^{Ar}), 134.8 (CH^{Ar}), 133.7 ($C^{Ar\text{-}q}$), 133.1 (CH^{Ar}), 131.6 (CH^{Ar}), 130.2 ($C^{Ar\text{-}q}$), 128.1 (CH^{Ar}), 123.1 (CH^{Ar}), 121.4 (CH^{Ar}), 120.9 (C=*C*), 119.8 (q, J_{CF} = 331.5 Hz, $2CF_3$), 85.1 (CTf_2), 37.5 (CH_2), 25.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.5 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 3451 (NH), 1685 (C=O), 1365, 1101 (O=S=O), 1207 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{14}F_6NO_6S_3$ [*M* + H]$^+$: 561.98819; found: 561.98847.

Triflyl-2,5-dihydropyrano[3,2-*b*]indole 77b. From 35 mg (0.06 mmol) of alkynone **71b**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **77b** (22 mg, 83%) as a yellow solid; mp 152–154ºC; ^{1}H NMR (700 MHz, $CDCl_3$, 50 ºC): δ = 8.34 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.78 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.67 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 7.64 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.52 (d, 1H, *J* = 1.9 Hz, CH^{Ar}), 7.40 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.17 (dd, 1H, *J* = 4.9, 3.4 Hz, CH^{Ar}), 5.35 (s, 2H, OCH_2), 1.91 (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$, 50 ºC): δ = 170.0 (NC=O), 156.9 ($C^{Ar\text{-}q}$), 155.8 ($C^{Ar\text{-}q}$), 142.2 ($C^{Ar\text{-}q}$), 135.1 (CH^{Ar}), 132.5 (CH^{Ar}), 131.7 (CH^{Ar}), 127.3 (CH^{Ar}), 124.7 (CH^{Ar}), 122.6 (*C*=C-Tf), 120.9 (CH^{Ar}), 120.3 (q, J_{CF} = 327.2 Hz, CF_3), 117.7 ($C^{Ar\text{-}q}$), 116.8 (CH^{Ar}), 100.1 (C=*C*-Tf), 69.6 (OCH_2), 25.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.5 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1665 (C=O), 1362, 1108 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{13}F_3NO_4S_2$ [*M* + H]$^+$: 428.02326; found: 428.02427. CCDC 1817363 contains the supplementary crystallographic data for compound **77b** in this paper. These data can be

obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Bis(triflyl)cyclobutene 78c. From 30 mg (0.09 mmol) of alkynone **70c**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **78c** (48 mg, 83%) as a yellow solid; mp 109–111ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 10.62 (s, 1H, NH), 8.48 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.79 (dd, 1H, *J* = 8.0, 1.3 Hz, CH^{Ar}), 7.52 (m, 3H, $3CH^{Ar}$), 6.92 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 6.81 (m, 2H, $2CH^{Ar}$), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 191.5 (C=O), 161.9 ($C^{Ar\text{-}q}$-OMe), 154.0 (NC=O), 141.9 ($C^{Ar\text{-}q}$), 141.5 (*C*=C), 138.6 ($C^{Ar\text{-}q}$), 136.6 (CH^{Ar}), 132.6 (CH^{Ar}), 130.9 ($2CH^{Ar}$), 122.1 (CH^{Ar}), 120.5 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.4 Hz, $2CF_3$), 119.4 (CH^{Ar}), 114.2 ($2CH^{Ar}$), 85.4 (CTf_2), 55.3 (OCH_3), 52.5 (OCH_3), 36.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.5 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 3449 (NH, OH), 1768 (C=O), 1355, 1102 (O=S=O), 1205 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{18}F_6NO_8S_2$ [*M* + H]$^+$: 602.03725; found: 602.03958.

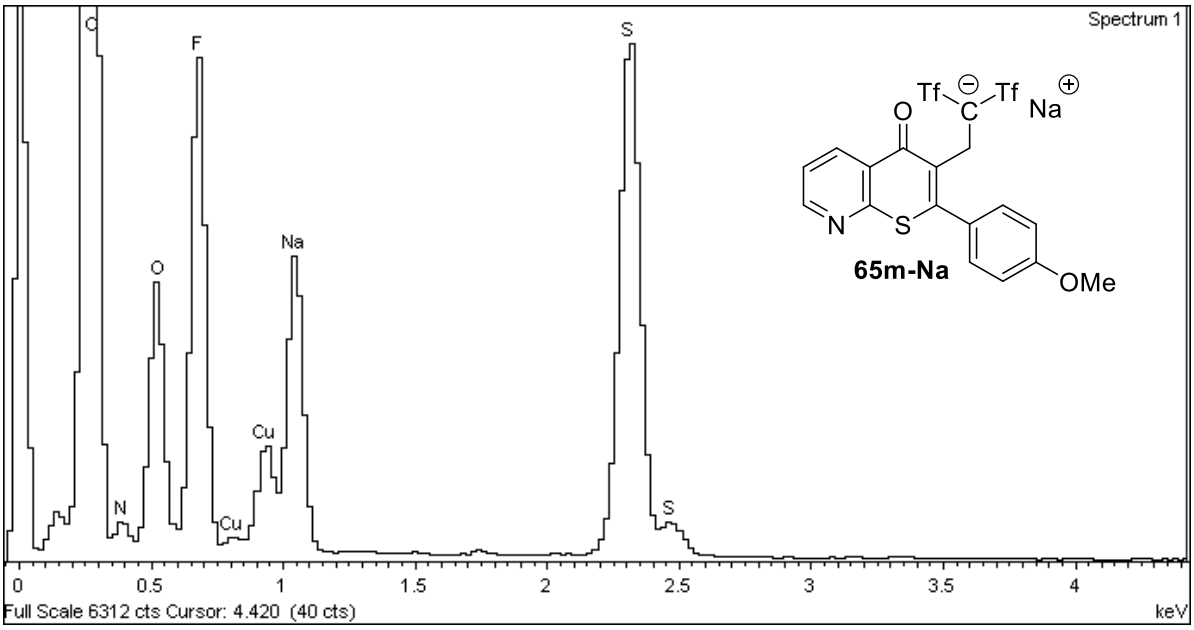
Triflyl-2,5-dihydropyrano[3,2-*b*]indole 77c. From 80 mg (0.13 mmol) of alkynone **70c**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 85:15) as eluent gave compound **77c** (50 mg, 81%) as a yellow solid; mp 142–144ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 50 ºC): δ = 8.20 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 7.76 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.59 (t, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.38 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.23 (m, 2H, $2CH^{Ar}$), 6.94 (m, 2H, $2CH^{Ar}$), 5.29 (s, 2H, OCH_2), 3.86 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 50 ºC): δ = 161.0 ($C^{Ar\text{-}q}$-OMe), 153.9 (C=O), 152.0 ($C^{Ar\text{-}q}$), 150.8 ($C^{Ar\text{-}q}$), 140.7 ($C^{Ar\text{-}q}$), 131.1 ($2CH^{Ar}$), 131.0 (CH^{Ar}), 125.0 ($C^{Ar\text{-}q}$), 124.2 (CH^{Ar}), 121.8 (*C*=C-Tf), 120.5 (CH^{Ar}), 120.3 (q, J_{CF} = 327.3 Hz, CF_3), 117.8 ($C^{Ar\text{-}q}$), 115.9 (CH^{Ar}), 113.1 ($2CH^{Ar}$), 100.1 (C=*C*-Tf), 69.2 (OCH_2), 55.3 (OCH_3), 53.6 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.0 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1762 (C=O), 1361, 1110 (O=S=O), 1209 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{21}H_{17}F_3NO_6S$ [*M* + H]$^+$: 468.07232; found: 468.07389.

Triflyl-2,5-dihydropyrano[3,2-*b*]indole 77d. From 20 mg (0.05 mmol) of alkynone **70d**, and after flash chromatography of the residue using hexanes/ethyl acetate (85:15 → 7:3) as eluent gave compound **77d** (18 mg, 64%) as a yellow solid; mp 121–123ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 50 ºC): δ = 8.11 (d, 1H, *J* = 8.5 Hz, CH^{Ar}), 7.58 (m, 2H, $2CH^{Ar}$), 7.49 (m, 1H, CH^{Ar}), 7.43 (m, 2H, $2CH^{Ar}$), 7.36 (m, 3H, $3CH^{Ar}$), 7.30 (m, 2H, $2CH^{Ar}$), 7.07 (m, 2H, $2CH^{Ar}$), 5.17 (s, 2H, OCH_2), 2.31 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 50 ºC): δ = 158.3 ($C^{Ar\text{-}q}$), 153.4 ($C^{Ar\text{-}q}$), 145.2 ($C^{Ar\text{-}q}$), 143.2 ($C^{Ar\text{-}q}$), 132.5 ($C^{Ar\text{-}q}$), 132.0 ($C^{Ar\text{-}q}$), 131.1 (CH^{Ar}), 130.8 ($2CH^{Ar}$), 130.0 (CH^{Ar}), 129.1 ($2CH^{Ar}$), 127.2 ($2CH^{Ar}$), 127.0 ($2CH^{Ar}$), 125.8 (CH^{Ar}), 123.4 (*C*=C-Tf), 120.8 (CH^{Ar}), 120.1 (q, J_{CF} = 326.9 Hz, CF_3), 118.4 (CH^{Ar}), 102.2 (C=*C*-Tf), 69.7 (OCH_2), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.8 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1371, 1107 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{25}H_{19}F_3NO_5S_2$ [*M* + H]$^+$: 534.06513; found: 534.06779.

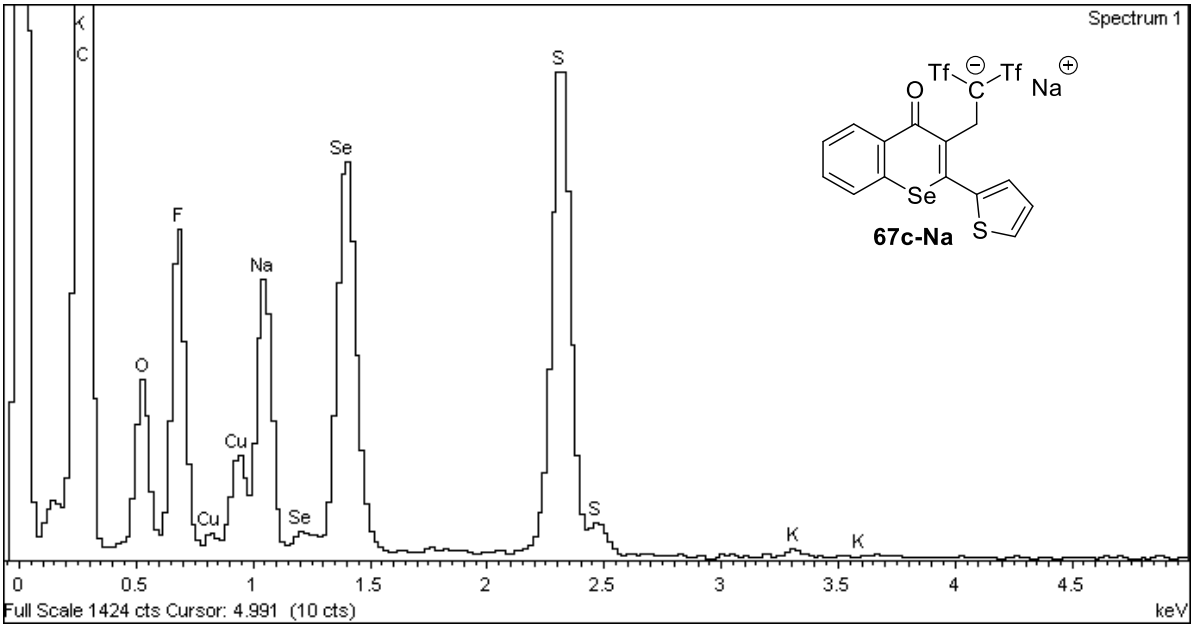
Triflyl-2,5-dihydropyrano[3,2-*b*]indole 77e. From 60 mg (0.16 mmol) of alkynone **70e**, and after flash chromatography of the residue using hexanes/ethyl acetate (85:15 → 7:3) as eluent gave compound **77e** (61 mg, 72%) as a yellow solid; mp 115–117ºC; ^{1}H NMR (500 MHz, $CDCl_3$, 50 ºC): δ = 7.82 (m, 2H, $2CH^{Ar}$), 7.75 (m, 2H, $2CH^{Ar}$), 7.71 (s, 1H, CH^{Ar}), 7.61 (t, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.45 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.40 (t, 1H, *J* = 8.4 Hz, CH^{Ar}), 7.19 (m, 2H, $2CH^{Ar}$), 5.37 (s, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 50 ºC): δ = 159.0 ($C^{Ar\text{-}q}$-OMe), 156.1 ($C^{Ar\text{-}q}$), 152.3 ($C^{Ar\text{-}q}$), 142.4 ($C^{Ar\text{-}q}$), 135.1 ($C^{Ar\text{-}q}$), 131.0 (CH^{Ar}), 130.2 (CH^{Ar}), 130.1 (CH^{Ar}), 128.5 (CH^{Ar}), 127.9 ($C^{Ar\text{-}q}$), 127.4 ($C^{Ar\text{-}q}$), 125.4 (CH^{Ar}), 125.3 (CH^{Ar}), 123.8 (*C*=C-Tf), 121.2 (CH^{Ar}), 120.1 (q, J_{CF} = 327.0 Hz, CF_3), 119.9 ($C^{Ar\text{-}q}$), 119.6 (CH^{Ar}), 116.8 (CH^{Ar}), 106.0 (CH^{Ar}), 103.0 (C=*C*-Tf), 69.4 (OCH_2), 55.4 (OCH_3), 39.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.9 (s, 3F, CF_3); IR ($CHCl_3$): ν

= 1369, 1107 (O=S=O), 1210 (C-F) cm^{-1}; HRMS (ES): calcd for $C_{24}H_{19}F_3NO_6S_2$ [*M* + H]$^+$: 538.06004; found: 538.06052.

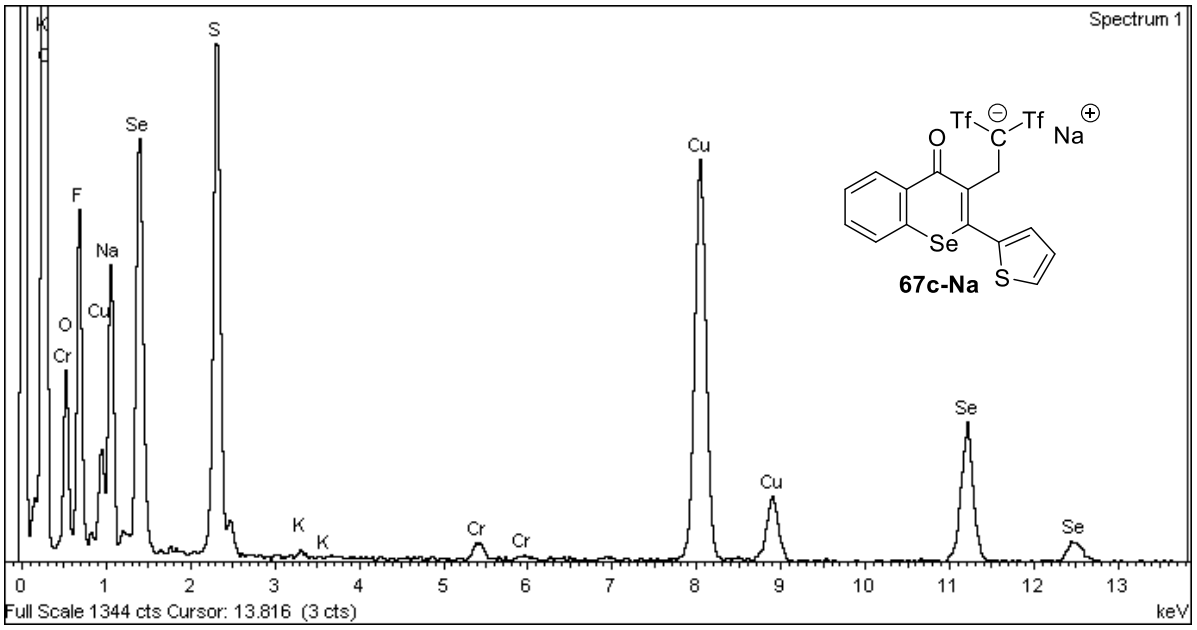
EDX-Spectra:



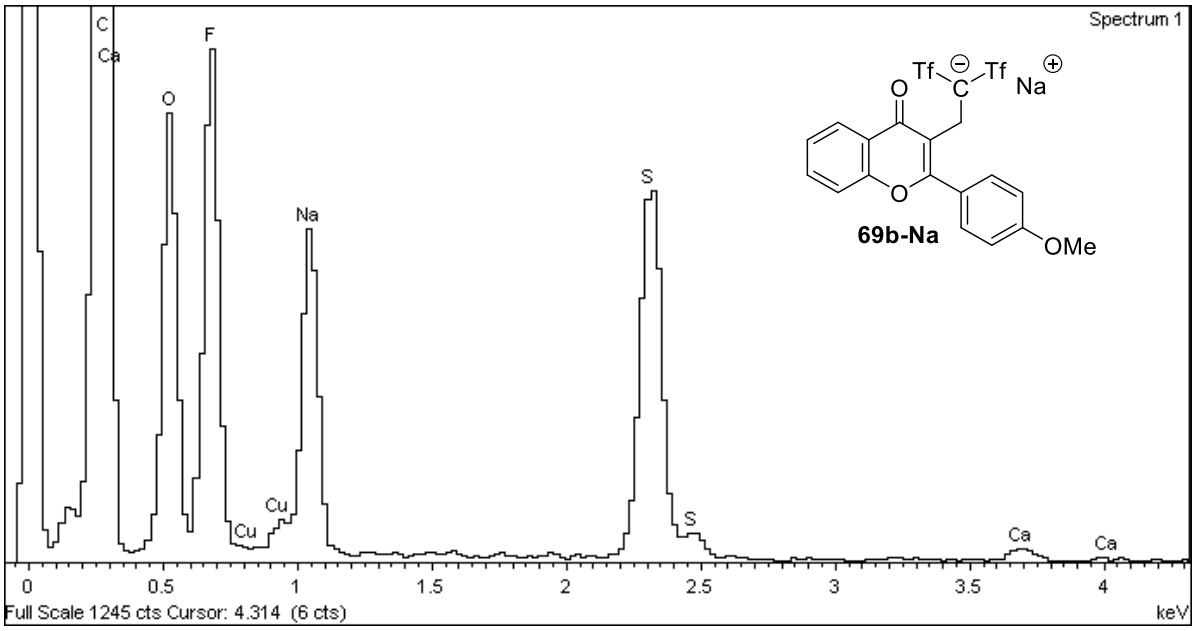
65m-Na EDX pattern. Copper cell.



67c-Na EDX pattern. Copper cell.



67c-Na EDX pattern. Chromium cell.



69b-Na EDX pattern. Copper cell.

VI.4. Notes and references

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8 CCDC 1528521 contains the supplementary crystallographic data for compound **71a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

9 CCDC 1815354 contains the supplementary crystallographic data for compound **76e** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10 CCDC 1817363 contains the supplementary crystallographic data for compound **77b** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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IX. CAPÍTULO 6

IX.1. Synthesis and Characterization of Stable Phosphorus Carbabetaines

Phosphorus 1,3- and 1,4-carbabetaines with 'P(+)−C−C(−)' and 'P(+)−C−C−C(−)' structures, respectively, in which the carbanion moiety was significantly stabilized by two trifluoromethylsulfonyl groups, have been synthesized and characterized. Analysis of their X-ray crystal structures revealed that any attractive interactions between the anionic and cationic moieties were negligibly weak. This result was corroborated by using natural bond orbital (NBO) and Bader's quantum theory of atoms in molecules (QTAIM) models. In contrast, performing the same analysis of a known 1,3-carbabetaine equivalent, which can be drawn as a 'P(+)−C−C=C−O(−)' resonance structure, revealed pronounced charge-transfer interactions between the anionic and cationic moieties.

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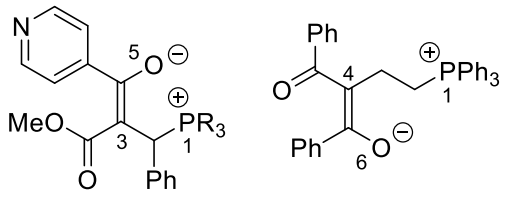
IX.2. Article

IX.2.1. Introduction

Phosphorus betaines are an important class of compounds in terms of their structure, properties, and reactivity.[1] Throughout the history of the Wittig reaction, 1,4-phosphonium oxides (1,4-oxabetaines),[2] which have a 'P$^+$−C−C−O$^-$' structure,[3] have been the subject of fierce discussion, because only four membered oxaphosphetanes have been detected in a Wittig reaction mixture by using NMR spectroscopy.[4] Free 1,4-oxabetainesare highly unstable and, to the best of our knowledge, have only been isolated once, by Ionkin et al. in 2007.[5,6] In contrast, there have been a number of reports of the isolation of thiolate analogues, because the P−S bond is thermodynamically weaker than the P−O bond.[1] In this context, 1,3- and 1,4-phosphonium alkanides (carbabetaines), which have 'P$^+$−C−C−' and 'P$^+$−C−C−C$^-$' structures, respectively, are particularly interesting. Some structural equivalents, as exemplified by compounds **79**[7,8] and **80**,[9] have been isolated (Figure IX.1).



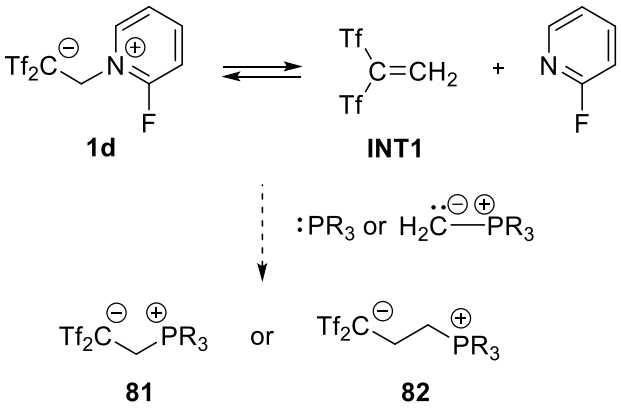
R = Me (**79a**), Bu (**79b**) **80**

Figure IX.1. Structures of previously reported carbabetaine equivalents.

However, in both cases, the "enolate" resonance structure contributes more to the anionic moiety than the "acylcarbanion" resonance structure. Therefore, these compounds should be considered as a type of oxabetaine, rather than as carbabetaines. Such 1,5-oxabetaines have also been regarded as generally unstable, because they undergo rapid ring-closure and afford pentavalent 1,2-oxaphospholenes. In fact, a number of such five-membered compounds have been characterized.[10] In the case of compound **79**, the betaine structure was determined by using single-crystal X-ray diffraction data; however, its geometry still implied the presence of some interactions between the anionic oxygen atom and the cationic

phosphorus atom. On the other hand, the crystallographic structure of 1,6-oxabetaine **80** has not yet been reported in the literature.

We are interested in the synthesis of zwitterions that contain a highly stabilized $[Tf_2C]^-$ moiety and their application as synthetic reagents and catalysts.[11] Recently, we found that 2-fluoropyridinium salt **1d** was an effective reagent for the *in situ* generation of highly electrophilic 1,1-bis(trifluoromethylsulfonyl)-ethylene **INT1** (Scheme IX.1) and was successfully applied to the synthesis of a superacidic carbon acid, denoted as Tf_2CHR.[12]

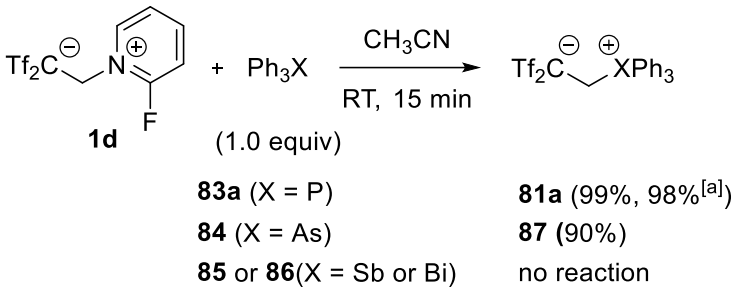


Scheme IX.1. *In situ* generation of $Tf_2C{=}CH_2$ **INT1** and this work. Tf=trifluoromethylsulfonyl.

Cycloaddition reactions of *in-situ*-generated compound **INT1** with 1,3-dienes,[12b,13] alkynes,[14] and organic azides[15] also proceeded smoothly to produce the corresponding triflones. Although 2-fluoropyridinium salt **1d** rapidly formed an equilibrium mixture of compound **INT1** and 2-fluoropyridine in MeCN, the reagent itself is a shelf-stable and easy-to-handle crystalline solid. In this context, we were interested in the reactions of compound **1d** with phosphorus-containing nucleophiles. Herein, we report the synthesis of 1,3- and 1,4-carbabetaines through the reaction of salt **1d** with phosphines or phosphonium ylides. Our phosphorus betaines, $R_3P^+{-}(C)_n{-}\ [CTf_2]^-$ (*n*=1, 2), were easily isolable and stable, and could be considered as the more-pronounced carbabetaines. Research achievements with Tf_2CHR compounds have stimulated the development of new organocatalysts that contain Tf_2CH groups as a strongly acidic functionality.[16,17] In such catalytic systems, it has been proposed that bulky and chemically inert $[Tf_2CR]^-$ groups endow cationic reaction intermediates with extremely high electrophilicity. This work will also provide fundamental insight into such catalytic systems.

IX.2.2. Results and discussion

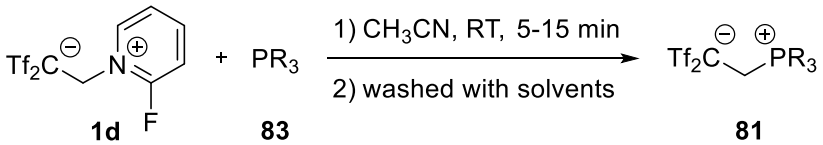
First, we examined the reactions of 2-fluoropyridinium salt **1d** with Ph_3P and Ph_3As as Group 15 nucleophiles (Scheme IX.2).

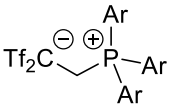


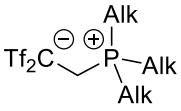
Scheme IX.2. Reactions of 2-fluoropyridinium salt **1d** with Ph_3P, Ph_3As, Ph_3Sb, and Ph_3Bi. [a] The yield of compound **81a** from the reaction with $Tf_2CHCH_2CHTf_2$ is given in parentheses.

When compound **1d** was treated with 1.0 equivalent of Ph_3P **83a** in MeCN, the reaction was complete within 15 minutes at room temperature to form the desired *P*-alkylation product **81a**, which was isolated in 99% yield by washing the crude material with CH_2Cl_2. Likewise, Ph_3As **84** was converted into the corresponding betaine **87** in 90% yield. In contrast, reactions with Sb **85** and Bi **86** analogues did not give any products, even on heating at reflux. Two other methods for the generation of compound **INT1** have been reported: a retro-Michael reaction of $Tf_2CHCH_2CHTf_2$[18] and a self-promoted condensation reaction of Tf_2CH_2 with formaldehyde.[13] Under the former set of conditions, compound **81a** was formed in 98% yield, whereas no product formation was observed under the latter set of conditions. Notably, compound **81a** was stable and thermal decomposition in boiling toluene was not observed.

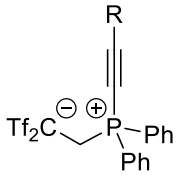
Under similar conditions, we performed the reactions of 2-fluoropyridinium salt **1d** with a range of phosphines (Scheme IX.3).

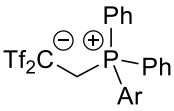




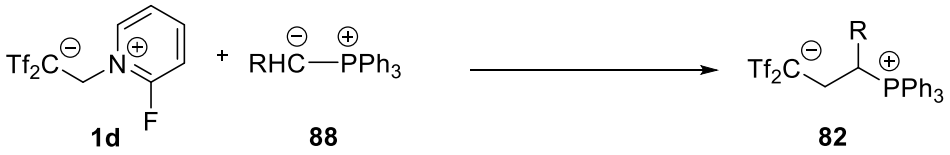


81b (Ar = 3,5-$Me_2C_6H_3$)	95%	**81j** (Alk = *n*-Bu)	94%
81c (Ar = 4-$MeOC_6H_4$)	80%	**81k** (Alk = *t*-Bu)	96%
81d (Ar = 2-MeC_6H_4)	97%		
81e (Ar = 2,4-$Me_2C_6H_3$)	89%		
81f (Ar = 2-$MeOC_6H_4$)	93%		
81g (Ar = 2-furyl)	95%		





		81l (R = Ph)	99%
		81m (R = 4-$MeOC_6H_4$)	94%
81h (Ar = 4-MeC_6H_4)	96%	**81n** (R = *n*-Bu)	99%
81i (Ar = 2-MeC_6H_4)	93%	**81o** (R = Si^iPr_3)	97%



88a (R = H)	THF, 0 °C to RT, 2 h	**82a** 62%
88b (R = CO_2Et)	CH_3CN, RT, 1 h	**82b** 68%

Scheme IX.3. Synthesis of 1,3-carbabetaine **81** and 1,4-carbabetaine **82**. Yields of isolated compounds are reported.

Triarylphosphines **83**, including derivatives that contained a bulky 2-substituted phenyl group(s), gave the corresponding *P*-alkylated products **81b–i** in excellent yields. Likewise, trialkylphosphonium products **81j** and **81k** were obtained from the reactions of salt **1d** with *n*Bu_3P and *t*Bu_3P, respectively. Sterically less-hindered alkynyldiphenylphoshines were also converted into the desired products **81l–o**, with aryl, alkyl, and trialkylsilyl substituents on the C(sp) atom. Notably, in these cases, the [2+2] cycloaddition products were not formed.[14a,b] In contrast, *in-situ*-generated compound **INT1** did not form any adducts during the reactions with some sulfides. To obtain structurally related 1,4-carbabetaines **82**, we examined the

reactions with phosphorus ylides **88**. Upon treatment of salt **1d** with an unstabilized ylide **88a** that was derived from methyltriphenylphosphonium bromide and *n*BuLi, the desired adduct **82a** was obtained in 62% yield. Likewise, a stabilized ylide **88b** was converted into adduct **82b**. The ^{31}P NMR chemical shift of tributylphosphonium **81j** (δ = 33.1 ppm) was very close to that of previously reported betaine **79b** (δ = 32.3 ppm).[7] ^{13}C NMR analysis of compounds **81** and **82** revealed the presence of anionic carbon atoms as singlets at δ = 55.5–60.5 and 62.9–63.1 ppm, respectively. These data suggested that all of the products could be considered as pronounced carbabetaines, as further evidenced by experimental and theoretical analyses of selected compounds.

We performed X-ray crystallographic analysis of nine compounds: 1,3-carbabetaines **81a**, **81e**, **81f**, **81i**, **81l**, **81m**, and **87**; and 1,4-carbabetaines **82a** and **82b**. The structures of compounds **81a**, **81i**, and **82a** are shown as representative examples in Figure IX.2 and their key parameters are summarized in Table IX.1.

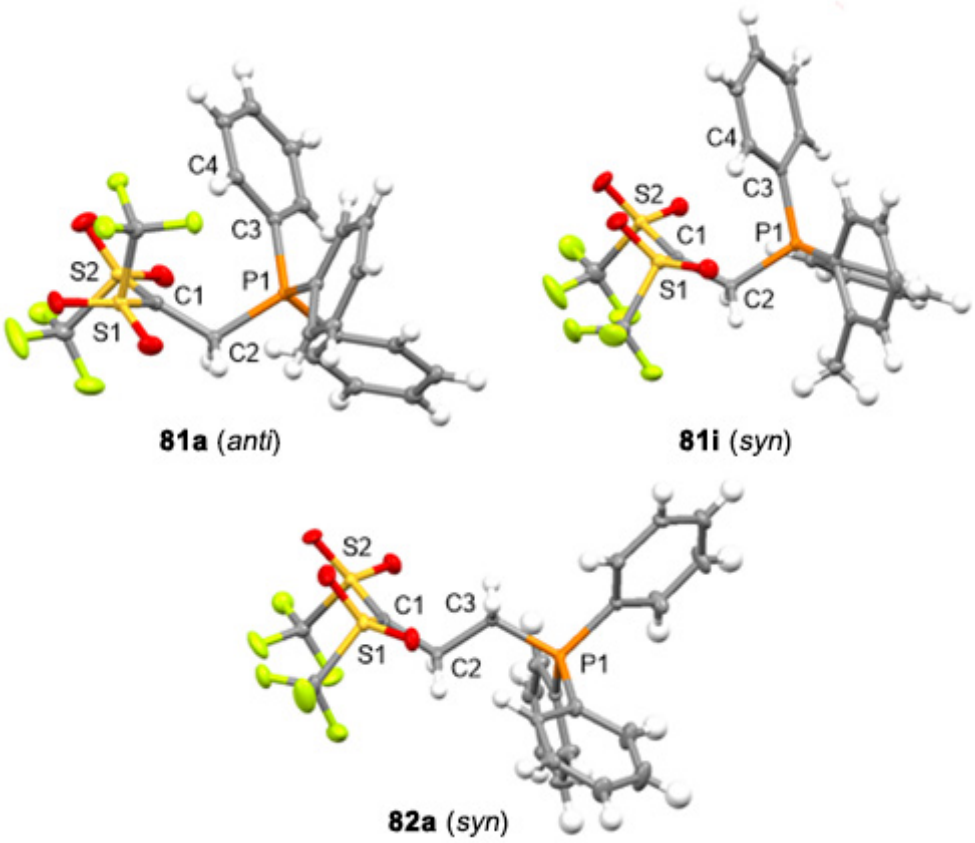


Figure IX.2. Crystallographic structures of compounds **81a**, **81i**, and **82a**; thermal ellipsoids are set at 50% probability.

Compound		C1−C2 [pm]	C2−P1 [pm]	C2−S [pm][a]	C2−P1 [pm][b]	C2−C2−P1 [°]
81a	expt.	150.9(4)	184.6(3)	168.6(3)	185.6(3)	117.2(2)
				168.7(3)	185.7(4)	
	calcd	149.2	185.1	169.5	186.3	115.2
				170.6	187.2	
81i	expt.	150.5(3)	185.3(2)	164.5(2)	184.6(2)	117.6(1)
				168.3(2)	184.4(2)	
	calcd	149.1	187.5	169.1	186.5	114.1
				170.1	186.1	
82a	exp.	152.5(6)	181.0(5)[c]	168.1(5)	186.0(6)	−
				167.8(6)	185.8(5)	

Table XI.1. Interatomic distances and angles in compounds **81a**, **81i**, and **82a**, based on X-ray crystallographic analysis and DFT calculations. [a] C1−S1 (top) and C1−S2 (bottom) distances; [b] S1−C(F_3) (top) and S2−C(F_3) (bottom) distances; [c] C3−P1 distance.

In all cases, a planar geometry of the anionic C1 atom and a tetrahedral structure of the cationic P1 atom were observed, which suggested that any direct interatomic interaction between the C1 and P1 atoms was negligibly weak, at least in the crystalline environment. In particular, in 1,4-carbabetaines **82a** and **82b**, an antiperiplanar orientation around the C2−C3 bond would make any intramolecular interactions ineffective. The stereochemistry of the two CF_3 groups relative to the plane of the C1 atom was another interesting structural feature: the two CF_3 groups adopted an *anti* conformation in compounds **81a**, **81l**, **81m**, and **81b**, but adopted a *syn* conformation in compounds **81e**, **81f**, **81i**, **82a**, and **87**. Similar to our previous work,[11,12a] the interatomic distances between the C1 atom and the S1/S2 atoms in all of the structures were notably shorter than the S−C(F_3) distances. This conformational behavior of the two CF_3 groups and the bond lengths in the $[Tf_2C]^-$ group confirmed delocalization of the electron lone pairs on the C1 atom to the $\sigma^*_{S–C(F3)}$ orbitals, which is known as negative hyperconjugation.

To obtain an accurate understanding of the electronic states in the carbabetaines, we optimized the experimental geometries of *anti* conformer **81a** and *syn* conformer **81i** by using hybrid DFT calculations at the M06-2x level of theory with the 6-311++G(d,p) basis set (Table 1).[19] The potential-energy minima were

established in combination with frequency analysis. Natural bond orbital (NBO) theory[20] and Bader's quantum theory of atoms in molecules (QTAIM)[21] were applied to the optimized geometries. For compound **81a**, the natural population analysis (NPA) charge of the C1 atom was calculated to be −0.93 *e* (for atom numbering, see Figures 2 and 3). According to the QTAIM analysis, the charge was −0.46 *e*. On the other hand, the charge on the P1 atom was +1.60 *e* and +2.46 *e* from the NBO and QTAIM analysis, respectively. Similar magnitudes of the atomic charges were obtained for compound **81i**. These values were consistent with the anionic and cationic character of the respective moieties. In both compounds **81a** and **81i**, NBO calculations revealed a porbital (LP_{C1}) at the C1 atom with suitable electron occupancy (**81a**: *1.69 e*; **81i**: *1.68 e*). In this case, the second-order perturbation of the LP_{C1} orbital to adjacent $\sigma^*_{S–C(F3)}$ orbitals was notably strong (stabilization energy >20 kcal mol^{-1}). This result supported the importance of negative hyperconjugation. In addition, the natural localized molecular orbital (NLMO)/NPA bond order of the C1−S bond was larger than those of the S−C(F_3) bonds (C1−S: 0.92–0.95; S−C(F_3): 0.72–0.75). The same trend was observed in the QTAIM analysis; for example, a larger electron density (ρ_{BCP}) and larger negative Laplacian ($\nabla^2\rho_{BCP}$) at the bond critical point (BCP) were observed, as well as a larger delocalization index. Note that the delocalization of the LP_{C1} bond to the sulfonic oxygen atoms was a subordinate stabilizing effect. The bond order of the S−O bond in organic sulfones was typically less than 1.5 (not 2), as mentioned in both theoretical and experimental studies.[22] In other words, the contribution of a widely accepted "S=O" resonance structure was significantly limited. The $LP_{C1}/\sigma^*_{C2–P1}$ interactions in compounds **81a** and **81i** were 12.9 and 17.6 kcal mol^{-1}, respectively. In light of the NBO analysis of the pyridinium zwitterion, this interaction was about 1.5-times weaker than the $LP_{C(–)}/\sigma^*_{C–N(+)}$ interaction.

The QTAIM analysis is a powerful tool for analyzing relatively weak interactions. For both compounds **81a** and **81i**, bond paths from the anionic C1 atom to the P1 atom, as well as to the sulfonic oxygen atoms, were not found (Figure IX.3).

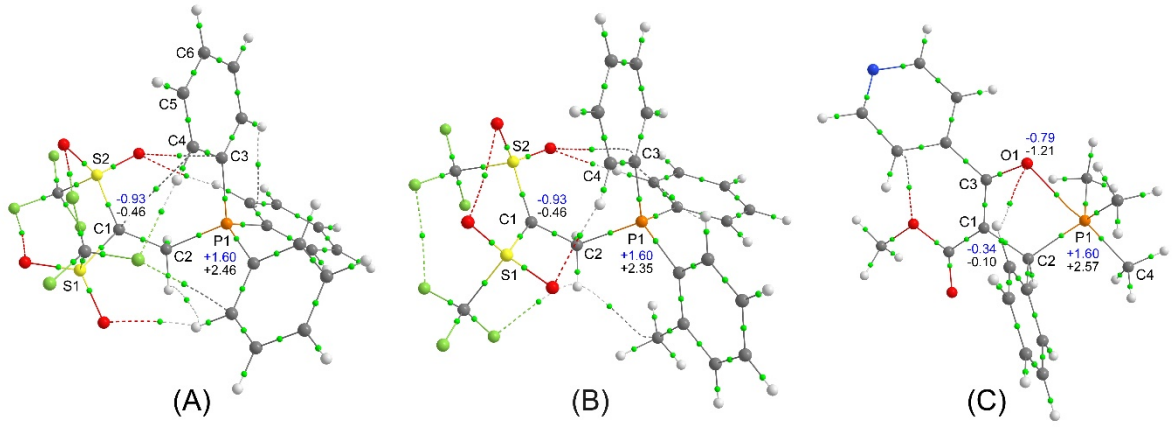


Figure IX.3. Bond critical points (green spheres) from the QTAIM analysis and key atomic charges (top: NPA charge; bottom: QTAIM charge) for A) **81a**; B) **81i**; and C) **79a**.

Beyond the bond paths for covalent bonds, a bond path from the C1 atom to the C4 atom in the phenyl group was only observed in compound **81a**. Based on its bond parameters (ρ_{BCP}, 0.0090 *e* bohr^{-3}; $\nabla^2\rho_{BCP}$, 0.0260 *e* bohr^{-5}; total electron energy density K_{BCP}, –0.00008), we observed slight charge-transfer (CT) character.[23] In the NBO analysis, a weak $LP_{C1}/\pi^*_{C4–C5}$ interaction (1.3 kcal mol^{-1}) was also observed. In addition, some bond paths from the sulfonic oxygen or fluorine atoms to the hydrogen or carbon atoms on the aryl groups were observed in both cases. In contrast, QTAIM analysis of phosphonium enolate **79a**[7] as a reference compound exhibited a pronounced bond path between the O1 and P1 atoms, which could be clearly classified as a CT interaction based on its bond parameters (ρ_{BCP}, 0.0519 *e* bohr^{-3}; $\nabla^2\rho_{BCP}$, 0.0724 *e* bohr^{-5}; K_{BCP}, 0.0108). In the optimized structure of compound **79a**, the P1 atom adopted a pseudotrigonal-bipyramidal structure. As shown in Figure IX.4, the $\nabla^2\rho_{BCP}$ contours and the overlap of the LP_{O1} and $\sigma^*_{P1–C4}$ orbitals, with a stabilization energy of 20.1 kcal mol^{-1}, allow the visualization of this interaction.

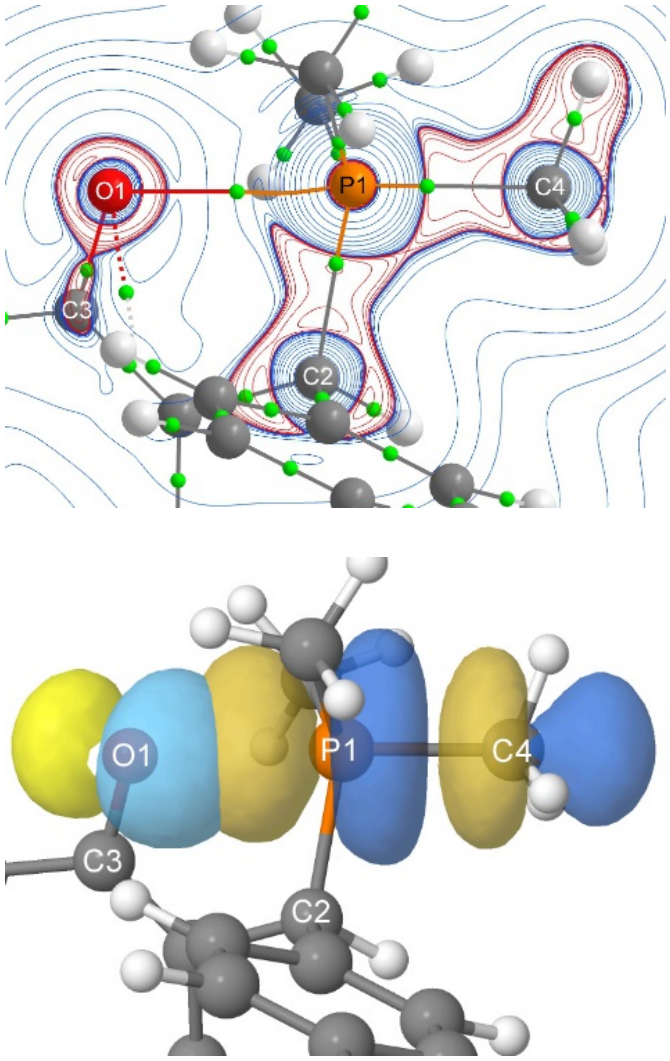


Figure IX.4. QTAIM and NBO projections of the O1···P1−C4 interactions in compound **79a**: A) positive (red) and negative (blue) Laplacians; B) overlap between the $LP(2)_{O1}$ and σ^*_{P1-C4} orbitals.

To understand such a sharp contrast, steric congestion around the phosphorus atom should also be considered. Therefore, we also analyzed diphenyl(phenylethynyl) and trimethyl derivatives **81l** and **81a-Me**, respectively. In both cases, there were no bond paths to the phosphorus atom, not only from the anionic carbon atom, but also from the oxygen and fluorine atoms. The lack of direct bond paths between the anionic carbon atoms and the cationic phosphorus atoms did not preclude the existence of any attractive interactions between the anionic and cationic parts.[24] This analyses revealed a number of weak noncovalent interactions between the R_3P^+ and the $[Tf_2C]^-$ groups, sometimes termed "anion···π" and

"anion···H−C" interactions,[25] which served as a stabilizing factor of the structures. In the $[Tf_2C]^-$ structure, negative hyperconjugation, as well as steric congestion around the anionic carbon atom, played a key role in suppressing direct CT interactions with the cationic phosphorus atom.

IX.2.3. Conclusion

We have successfully synthesized 1,3- and 1,4-carbabetaines **81** and **82** by using *in-situ*-generated $Tf_2C{=}CH_2$ **INT1**. X-ray crystallographic analyses of the products clearly showed that any attractive interactions between the cationic and anionic moieties were negligibly weak. Compared with reference compound **79a**, which exhibited a clear '$O^-\cdots P^+$' charge-transfer interaction, carbabetaines **81** and **82** did not exhibit any direct interatomic interactions between the anionic and cationic moieties by using NBO and QTAIM analyses. However, some weak interactions collectively served to stabilize their molecular structure. Based on these results, these compounds represent the first examples of well-defined carbabetaines. We have also provided greater insight into the stability of the $[Tf_2CR]^-$ ion. In particular, the importance of negative hyperconjugation in the stability of the $[Tf_2CR]^-$ anion was quantitatively established.

IX.3. Experimental Section

General Methods: All reactions were carried out under Ar atmosphere. Melting points were uncorrected. IR spectra were recorded on a Bruker ALPHA FTIR spectrometer. NMR spectra were recorded on a Bruker Avance III Nanobay 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, and 162 MHz for ^{31}P) or a Bruker Avance III 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) in $CDCl_3$ or CD_3CN. Data are reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sex = sextet, m = multiplet, br = broad), and coupling constants *J* given in Hz. Chemical shifts (in ppm) were referenced to solvent signal ($CDCl_3$, 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C; CD_3CN, 1.93 ppm for ^{1}H and 118.2 ppm for ^{13}C). For ^{19}F NMR spectroscopy, (trifluoromethyl)benzene (0 ppm) was used as an internal standard. For ^{31}P NMR spectroscopy, 85% phosphoric acid (0 ppm) was used as an external standard. Mass spectra were measured on a Micromass LCT mass spectrometer or a Waters Xevo G2-XS Tof by electrospray ionisation-time of flight (ESI-TOF).

Reaction of 2-fluoropyridinium salt 1d with group 15 nuclephiles. 2-Fluoropyridinium salt **1d** (38.0 mg, 97.6 mmol) was added to a solution of triphenyl coumpounds **83a**, **84**, **85** or **86** (101 mmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2 (3x2 mL) to give the product **81a** or **87**.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(triphenylarsonio)ethan-1-ide 87. To a solution of triphenylarsine **84** (61.8 mg, 202 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (74.2 mg, 191 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with $CHCl_3$ (3x2 mL) to give the product **87** in 90% yield (102 mg, 171 μmol). Colorless crystals (from EtOAc); Mp. 137-138°C, IR (ATR) ν = 3064, 1440, 1347, 1195, 1164, 1099, 1008, 737, 576 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ = 4.44 (2H, s), 7.61-7.68 (12H, m), 7.72-7.75 (3H, m); ^{13}C NMR (125 MHz, CD_3CN) δ = 34.9, 58.5, 122.0 (q, J_{CF} = 327 Hz), 123.9, 131.1, 134.3, one carbon was not observed owning to peak overlapping; ^{19}F NMR (376 Hz, CD_3CN) δ = –16.8 (6F, s); MS (ESI-TOF) *m/z* 599 $[M+H]^+$; HRMS calcd for $C_{22}H_{18}AsF_6O_4S_2$ $[M+H]^+$, 598.9767; found, 598.9772. Anal. CCDC-1833469 contains the supplementary crystallographic data for compound **87** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(triphenylphosphonio)ethan-1-ide 81a. 2-Fluoropyridinium salt **1d** (38.0 mg, 97.6 mmol) was added to a solution of triphenylphosphine **83a** (26.5 mg, 101 mmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with DCM (3x2 mL) to give the product **81a** in 99% yield (53.7 mg, 96.9 mmol). Colorless crystals (from $CHCl_3$); m.p. 238–240 ºC; ^{1}H NMR (500 MHz, CD_3CN): δ = 4.31 (br s, 2H), 7.63–7.71 (m, 12H), 7.80–7.87 ppm (m, 3H); ^{13}C NMR (125 MHz, CD_3CN): d = 30.0 (d, J_{CP} = 51.4 Hz), 57.8, 119.7 (d, J_{CP} = 84.2 Hz), 121.99 (q, J_{CP} = 327 Hz), 122.03 (q, J_{CP} = 328 Hz), 130.7 (d, J_{CP} = 12.5 Hz), 135.4 (d, J_{CP} = 9.3 Hz), 135.6 ppm (d, J_{CP} = 2.5 Hz); ^{19}F NMR (376 Hz, CD_3CN): δ = –16.3 ppm (s, 6F); ^{31}P NMR (162 Hz, CD_3CN): δ = 23.2 ppm; IR (ATR): ν = 2971, 1439, 1347, 1162, 1108, 994, 723, 688, 606, 488 cm^{-1}; MS (ESI-TOF) *m/z*: 555 $[M+H]^+$; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{17}F_6O_4PS_2$: 555.0288 $[M+H]^+$; found: 555.0286. CCDC-1833461 contains the supplementary crystallographic data for compound **81a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Reaction of 2-fluoropyridinium salt 1d with phosphines 83. 2-Fluoropyridinium salt **1d** (38.0 mg, 97.6 mmol) was added to a solution of phosphines **83** (101 mmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with the solvent or solvent mixture indicated in each case (3x2 mL) to give the 1,3-phosphocarbabetaines **81**.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(tris(3,5-dimethylphenyl)phosphonio)ethan-1-ide 81b. To a solution of tris(3,5-dimethylphenyl)phosphine **83b** (35.8 mg, 103 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (39.6 mg, 102 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane (3x2 mL) to give the product **81b** in 95% yield (61.7 mg, 96.7 μmol). Colorless crystals (from $CHCl_3$); Mp. 201-203°C; IR (ATR) ν = 2924, 1354, 1160, 1129, 1100, 1017, 764, 579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.38 (18H, s), 4.22 (2H, brs), 7.16 (3H, s), 7.19 (3H, s), 7.37 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4, 29.7 (q, J_{CP} = 52.3 Hz), 57.2, 118.5 (q, J_{CP} = 82.4 Hz), 120.95 (q, J_{CF} = 328 Hz), 120.99 (q, J_{CF} = 328 Hz), 131.7 (q, J_{CP} = 9.0 Hz), 136.4 (q, J_{CP} = 3.1 Hz), 139.7 (q, J_{CP} = 13.1 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.6 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 19.9; MS (ESI-TOF) *m*/*z* 661 $[M+Na]^+$; HRMS calcd for $C_{28}H_{29}F_6O_4PS_2$ $[M+Na]^+$, 661.1047; found, 661.1048. Anal. Calcd for $C_{28}H_{29}F_6O_4PS_2$: C, 52.66; H, 4.58. Found: C, 52.94; H, 4.84.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(tris(4-methoxyphenyl)phosphonio)ethan-1-ide 81c. To a solution of tris(4-methoxyphenyl)phosphine **83c** (36.1 mg, 102 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (39.1 mg, 100 mmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane/$CHCl_3$ (5:1, 3x1 mL) to give the product **81c** in 80% yield (51.7 mg, 80.2 μmol). Colorless crystals (from CH_2Cl_2); Mp 103-105°C.; IR (ATR) ν = 2927, 1604, 1350, 1165, 1100, 762, 611, 597, 576 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.89 (9H, s), 4.13 (2H, brs), 7.11 (6H, d, *J* = 8.3 Hz), 7.48-7.59 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 30.3 (d, J_{CP} = 54.5 Hz), 55.7, 56.8, 109.5 (d, J_{CP} = 92.0 Hz), 115.6 (d, J_{CP} = 13.4 Hz), 121.00 (q, J_{CF} = 328 Hz), 121.04 (q, J_{CF} = 328 Hz), 136.1 (d, J_{CP} = 10.7 Hz), 164.4 (d, J_{CP} = 2.9 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.7 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 19.7; MS (ESI-TOF) *m*/*z* 667 $[M+Na]^+$; HRMS calcd for $C_{25}H_{23}F_6NaO_7PS_2$ $[M+Na]^+$, 667.0425; found, 667.0421.

2-(Tri-*o*-tolylphosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81d. To a solution of tri-*o*-tolylphosphine **83d** (31.7 mg, 104 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (40.4 mg, 104 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with $CHCl_3$ (3x2 mL) to give the product **81d** in 97% yield (59.4 mg, 99.6 μmol). Colorless crystals (from $CHCl_3$); Mp. 182-185 °C; IR (ATR) ν = 2921, 1452, 1352, 1195, 1166, 1103, 756, 578, 475 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ = 2.18 (9H, s), 4.47 (2H, d, J_{HP} = 5.5 Hz), 7.41-7.50 (6H, m), 7.69 (3H, t, *J* = 7.6 Hz), 7.77 (3H, dd, J_{HP} = 13.9 Hz, J_{HH} = 8.8 Hz); ^{13}C NMR (125 MHz, CD_3CN) δ = 23.5 (d, J_{CP} = 2.5 Hz), 30.6 (d, J_{CP} = 48.8 Hz), 59.8, 118.8 (d, J_{CP} = 78.0 Hz), 122.01 (q, J_{CF} = 328 Hz), 122.04 (q, J_{CF} = 328 Hz), 127.6 (d, J_{CP} = 11.3 Hz), 134.5 (d, J_{CP} = 11.2 Hz), 135.4 (d, J_{CP} = 2.5 Hz), 136.7 (d, J_{CP} = 10.1 Hz), 145.2 (d, J_{CP} = 7.5 Hz); ^{19}F NMR (376 Hz, CD_3CN) δ = –15.4 (6F, s); ^{31}P NMR (162 Hz, CD_3CN) δ = 23.0; MS (ESI-TOF) *m*/*z* 619 $[M+Na]^+$; HRMS calcd for $C_{25}H_{23}F_6NaO_4PS_2$ $[M+Na]^+$, 619.0577; found, 619.0577.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(tris(2,4-dimethylphenyl)phosphonio)ethan-1-ide 81e. To a solution of tris(2,4-dimethylphenyl)phosphine **83e** (72.6 mg, 210 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (77.2 mg, 198 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with 3% $CHCl_3$ in hexane (5x2 mL) to give the product **81e** in 89% yield (113 mg, 177 μmol). Colorless crystals (from $CHCl_3$); Mp. 206-208°C; IR (ATR) ν = 1350, 1169, 1102, 762, 598, 577 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.20 (9H, s), 2.41 (9H, s), 4.39 (2H, brd, J_{HP} = 5.0 Hz), 7.20 (3H, d, J = 8.0 Hz), 7.20-7.26 (3H, m), 7.52-7.60 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4, 23.1 (d, J_{CP} = 2.4 Hz), 30.3 (d, J_{CP} = 51.4 Hz), 59.0, 114.7 (d, J_{CP} = 80.5 Hz), 121.0 (q, J_{CF} = 329 Hz), 121.1 (q, J_{CF} = 329 Hz), 127.6 (d, J_{CP} = 12.8 Hz), 134.4 (d, J_{CP} = 11.7 Hz), 135.4 (d, J_{CP} = 11.1 Hz), 143.7 (d, J_{CP} = 8.5 Hz), 145.4 (d, J_{CP} = 2.8 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –14.9 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 22.1; MS (ESI-TOF) *m*/*z* 661 $[M+Na]^+$; HRMS calcd for $C_{28}H_{29}F_6NaO_4PS_2$ $[M+Na]^+$, 661.1047; found, 661.1052. CCDC-1833463 contains the supplementary crystallographic data for compound **81e** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(tris(2-methoxyphenyl)phosphonio)ethan-1-ide 81f. To a solution of tris(2-methoxyphenyl)phosphine **83f** (36.6 mg, 104 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (40.0 mg, 103 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with $CHCl_3$ (3x2 mL) to give the product **81f** in 93% yield (61.6 mg, 95.6 μmol). Colorless crystals (from CH_2Cl_2); Mp. 256-258°C (decomp.); IR (ATR) ν = 1590, 1479, 1347, 1159, 1104, 1015, 763, 575, 504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.81 (9H, s), 4.71 (2H, d, J_{HP} = 7.5 Hz), 7.04 (3H, td, J = 7.5, 2.3 Hz), 7.09-7.13 (6H, m), 7.69 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.5 (d, J_{CP} = 50.0 Hz), 55.7, 58.8, 106.2 (d, J_{CP} = 86.0 Hz), 112.0 (d, J_{CP} = 6.9 Hz), 121.2 (d, J_{CP} = 12.0 Hz), 121.4 (q, J_{CF} = 329 Hz), 121.5 (q, J_{CF} = 329 Hz), 135.7 (d, J_{CP} = 7.5 Hz), 136.3 (d, J_{CP} = 1.8 Hz), 161.2 (d, J_{CP} = 2.7 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.7 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 29.1; MS (ESI-TOF) *m*/*z* 645 $[M+H]^+$; HRMS calcd for $C_{25}H_{24}F_6O_7PS_2$ $[M+H]^+$, 645.0605; found, 645.0601. Anal. Calcd for $C_{25}H_{23}F_6O_7PS_2$: C, 46.59; H, 3.60. Found: C, 46.53; H, 3.70. CCDC-1833465 contains the supplementary crystallographic data for compound **81f** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1,1-Bis((trifluoromethyl)sulfonyl)-2-(tris(2-methoxyphenyl)phosphonio)ethan-1-ide 81g,To a solution of tris(2-furyl)phosphine **83g** (24.0 mg, 103 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (39.2 mg, 101 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with $CHCl_3$ (3x2 mL) to give the product **81g** in 95% yield (50.0 mg, 95.4 μmol). Colorless crystals (from CH_3Cl); Mp. 145-147 °C; IR (ATR) ν = 2424, 1732, 1453, 1345, 1112, 1001, 764, 584 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.31 (2H, brs), 6.76-6.82 (3H, m), 7.51 (3H, d, J = 2.1 Hz), 8.02 (3H, d, J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.4 (d, J_{CP} = 54.1 Hz), 55.5, 113.2 (d, J_{CP} = 9.4 Hz), 120.89 (q, J_{CF} = 327 Hz), 120.94 (q, J_{CF} = 327 Hz), 130.5 (d, J_{CP} = 19.9 Hz), 131.1(d, J_{CP} = 138 Hz), 153.3 (d, J_{CP} = 8.4 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.95 (3F, s), –15.96 (3F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = –13.6; MS (ESI-TOF) *m*/*z* 525 $[M+H]^+$; HRMS calcd for $C_{16}H_{12}F_6O_7PS_2$ $[M+H]^+$, 524.9666; found, 524.9665.

2-(Diphenyl(*p*-tolyl)phosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81h. To a solution of diphenyl(*p*-tolyl)phosphine **81h** (28.7 mg, 104 μmol) in CH_3CN (1.0

mL), 2-fluoropyridinium salt **1d** (38.7 mg, 99.4 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with $CHCl_3$ (3x2 mL) to give the product **81h** in 96% yield (54.2 mg, 95.3 μmol). Colorless crystals (from CH_2Cl_2); Mp. 186-187 °C; IR (ATR) ν = 1438, 1347, 1150, 1096, 719, 594, 579, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.49 (3H, s), 4.27 (2H, brs), 7.40-7.57 (4H, m), 7.57-7.72 (8H, m), 7.73-7.84 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.8, 30.3 (d, J_{CP} = 51.7 Hz), 56.5, 114.7 (d, J_{CP} = 86.3 Hz), 118.8 (d, J_{CP} = 84.0 Hz), 121.0 (q, J_{CF} = 328 Hz), 122.1 (q, J_{CF} = 328 Hz), 129.9 (d, J_{CP} = 8.2 Hz), 130.8 (d, J_{CP} = 12.1 Hz), 134.2 (d, J_{CP} = 12.8 Hz), 134.3 (d, J_{CP} = 2.8 Hz), 134.7 (d, J_{CP} = 2.6 Hz), 146.2 (d, J_{CP} = 3.0 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.7 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 21.4; MS (ESI-TOF) *m/z* 591 $[M+Na]^+$; HRMS calcd for $C_{23}H_{19}F_6NaO_4PS_2$ $[M+Na]^+$, 591.0264; found, 591.0260.

2-(Diphenyl(o-tolyl)phosphonio)-1,1-bis((trifluoromethyl) sulfonyl)-ethan-1-ide 81i. 2-Fluoropyridinium salt **1d** (40.0 mg, 103 mmol) was added to a solution of diphenyl(o-tolyl)phosphine **83i** (28.4 mg, 103 mmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2 (3x2 mL) to give the product **81i** in 93% yield (54.4 mg, 95.7 mmol). Colorless crystals (from CH_2Cl_2); m.p. 212–214 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (3H , s), 4.35 (br s, 2H), 7.37–7.45 (m, 2H), 7.46–7.54 (m, 1H), 7.63–7.73 (m, 9H), 7.78–7.85 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.1 (d, J_{CP} = 3.8 Hz), 30.6 (d, J_{CP} = 48.1 Hz), 57.2, 117.8 (d, J_{CP} = 79.5 Hz), 118.1 (d, J_{CP} = 80.0 Hz), 120.95 (q, J_{CP} = 328 Hz), 120.99 (q, J_{CP} = 328 Hz), 127.2 (d, J_{CP} = 12.3 Hz), 130.0 (d, J_{CP} = 12.4 Hz), 133.6 (d, J_{CP} = 11.1 Hz), 134.5 (d, J_{CP} = 8.9 Hz), 134.8 (d, J_{CP} = 2.5 Hz), 134.9 (d, J_{CP} = 2.5 Hz), 135.4 (d, J_{CP} = 10.2 Hz), 143.0 ppm (d, J_{CP} = 9.0 Hz); ^{19}F NMR (376 Hz, $CDCl_3$): δ = –15.6 (s, 6F); ^{31}P NMR (162 Hz, $CDCl_3$): δ = 22.2 ppm; IR (ATR): ν = 1438, 1345, 1173, 1155, 1097, 719, 598, 578, 475 cm^{-1}; MS (ESI-TOF): *m/z*: 596 $[M+H]^+$; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{20}F_6O_4PS_2$: 569.0445 $[M+H]^+$; found: 569.0443; elemental analysis calcd (%) for $C_{23}H_{19}F_6O_4PS_2$: C 48.59, H 3.37; found: C 48.36, H 3.50. CCDC-1833464 contains the supplementary crystallographic data for compound **81i** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(Tributylphosphonio)-1,1-bis((trifluoromethyl)-sulfonyl)ethan-1-ide 81j. 2-Fluoropyridinium salt **1d** (78.7 mg, 202 mmol) was added to a solution of tributylphosphine **83j** (50 mL, 203 mmol) in MeCN (2.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with *n*-hexane (3x2 mL) to give the product **81j** in 94% yield (93.8 mg, 190 mmol). Colorless crystals (from CH_2Cl_2); m.p. 76.0–77.5 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 6.9 Hz, 9H), 1.45–1.59 (m, 12 H), 2.09–2.18 (m, 6H), 3.20 ppm (d, J_{CP} = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2, 18.9 (d, J_{CP} = 46.2 Hz), 21.4 (d, J_{CP} = 51.5 Hz), 23.2 (d, J_{CP} = 4.6 Hz), 23.8 (d, J_{CP} = 14.8 Hz), 56.1, 121.2 (q, J_{CP} = 328 Hz), 121.3 ppm (q, J_{CP} = 328 Hz); ^{19}F NMR (376 Hz, $CDCl_3$): δ = –15.2 ppm (s, 6F); ^{31}P NMR (162 Hz, $CDCl_3$): δ = 33.1 ppm; IR (ATR): ν = 2966, 2938, 1344, 1158, 1099, 999, 608, 576, 505 cm^{-1}; MS (ESI-TOF): *m/z*: 517 $[M+Na]^+$; HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{29}F_6NaO_4PS_2$: 517.1047 $[M+Na]^+$; found: 517.1038; elemental analysis calcd (%) for $C_{16}H_{29}F_6O_4PS_2$: C 38.86, H 5.91; found: C 38.96, H 5.78.

2-(Tri-*tert*-butylphosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81k. To a solution of tri-*tert*-butylphosphine **83k** (50 μL, 213 μmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (81.3 mg, 209 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane (3x2 mL) to give the product

81k in 96% yield (99.5 mg, 201 μmol). Colorless crystals (from $CHCl_3$); Mp. 90.0-92.0°C; IR (ATR) ν = 2988, 1484, 1350, 1190, 1151, 1098, 719, 577, 503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.74 (27H, d, J_{HP} = 13.5 Hz), 3.75 (2H, d, J_{HP} = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.8 (d, J_{CP} = 33.4 Hz), 30.5, 41.4 (d, J_{CP} = 23.4 Hz), 60.5, 121.39 (q, J_{CF} = 330 Hz), 121.43 (q, J_{CF} = 330 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –13.7 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 45.5; MS (ESI-TOF) *m*/*z* 495 $[M+H]^+$; HRMS calcd for $C_{16}H_{30}F_6O_4PS_2$ $[M+H]^+$, 495.1227; found, 495.1227.

2-(Diphenyl(phenylethynyl)phosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81l. To a solution of diphenyl(phenylethynyl)phosphine **83l** (30.0 mg, 0.104 μmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (40.8 mg, 0.104 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane/$CHCl_3$ (20:1, 3x2 mL) to give the product **81l** in 99% yield (60.0 mg, 0.103 mmol). Colorless crystals (from CH_3CN); Mp. 131-133°C; IR (ATR) ν = 2182, 1438, 1347, 1169, 1153, 1109, 1001, 686, 604, 502, 481 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.18 (2H, brs), 7.44 (2H, t, *J* = 7.6 Hz), 7.56 (1H, t, *J* = 7.6 Hz), 7.64-7.71 (4H, m), 7.76-7.81 (2H, m), 7.84-7.95 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 32.5 (d, J_{CP} = 58.4 Hz), 57.6, 68.4 (d, J_{CP} = 188 Hz), 117.69, 117.73, 119.5 (d, J_{CP} = 27.4 Hz), 120.9 (q, J_{CF} = 327 Hz), 121.0 (q, J_{CF} = 327 Hz), 128.9, 130.1 (d, J_{CP} = 13.2 Hz), 132.6, 132.7 (d, J_{CP} = 10.8 Hz), 133.5 (d, J_{CP} = 2.5 Hz), 135.0 (d, J_{CP} = 2.8 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.8 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 13.0; MS (ESI-TOF) *m*/*z* 579 $[M+H]^+$; HRMS calcd for $C_{24}H_{17}F_6O_4PS_2$ $[M+H]^+$, 579.0288; found, 579.0292. CCDC-1833466 contains the supplementary crystallographic data for compound **81l** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(((4-Methoxyphenyl)ethynyl)diphenylphosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81m. To a solution of (4-methoxyphenyl)ethynyl)diphenylphosphine **83m** (32.6 mg, 0.103 μmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (40.1 mg, 0.103 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane/$CHCl_3$ (20:1, 3x2 mL) to give the product **81m** in 94% yield (58.9 mg, 0.096 mmol). Colorless crystals (from CH_3CN); Mp. 171-173 °C; IR (ATR) ν = 2168, 1601, 1343, 1178, 1114, 1010, 787, 607, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.84 (3H, s), 4.16 (2H, brs), 6.94 (2H, d, *J* = 8.8 Hz), 7.62-7.69 (4H, m), 7.76 (2H, t, *J* = 7.9 Hz), 7.81 (2H, d, *J* = 8.8 Hz), 7.84-7.94 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 32.4 (d, J_{CP} = 50.3 Hz), 55.5, 57.7, 67.7 (d, J_{CP} = 191 Hz), 109.4 (d, J_{CP} = 4.8 Hz), 114.6, 120.5 (br), 120.90 (d, J_{CP} = 28.8 Hz), 120.93 (q, J_{CF} = 327 Hz), 121.0 (q, J_{CF} = 327 Hz), 130.0 (d, J_{CP} = 13.4 Hz), 132.7 (d, J_{CP} = 10.8 Hz), 134.8 (d, J_{CP} = 2.9 Hz), 135.7 (d, J_{CP} = 2.3 Hz), 163.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.9 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 12.6; MS (ESI-TOF) *m*/*z* 631 $[M+Na]^+$; HRMS calcd for $C_{25}H_{19}F_6NaO_5PS_2$ $[M+Na]^+$, 631.0213; found, 631.0216. CCDC-1833462 contains the supplementary crystallographic data for compound **81l** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(Hex-1-yn-1-yldiphenylphosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81n. To a solution of hex-1-yn-1-yldiphenylphosphine **83n** (27 mg, 0.101 μmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (39.3 mg, 0.101 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane/$CHCl_3$ (20:1, 3x2 mL) to give the product **81n** in 99% yield (56.0 mg, 0.100 mmol). Colorless crystals (from CH_3CN); Mp. 106-108°C, IR (ATR) ν = 2962, 2196, 1489, 1351, 1169, 1114, 688 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, t, J = 7.4 Hz), 1.49 (2H, sex, J = 7.4 Hz), 1.76 (2H, quint, J = 7.4 Hz), 2.70 (2H, td, J = 7.4 Hz), 4.07 (2H, brs), 7.61-7.69 (4H, m), 7.76 (2H, t, J = 7.7 Hz), 7.83 (4H, dd, J_{HP} = 13.2 Hz, J_{HH} = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.3, 20.4 (d, J_{CP} = 3.6 Hz), 22.1, 28.8 (d, J_{CP} = 1.6 Hz), 32.4 (d, J_{CP} = 62.8 Hz), 57.6, 61.1 (d, J_{CP} = 189 Hz), 120.2 (br), 120.9 (q, J_{CF} = 327 Hz), 121.0 (q, J_{CF} = 327 Hz), 125.6 (d, J_{CP} = 27.2 Hz), 130.0 (d, J_{CP} = 13.4 Hz), 132.6 (d, J_{CP} = 10.8 Hz), 134.8 (d, J_{CP} = 2.8 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –20.9 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 12.8; MS (ESI-TOF) *m*/*z* 559 $[M+H]^+$; HRMS calcd for $C_{22}H_{22}F_6O_4PS_2$ $[M+H]^+$, 559.0601; found, 559.0606.

2-(Diphenyl((triisopropylsilyl)ethynyl)phosphonio)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 81o. To a solution of diphenyl((triisopropylsilyl)ethynyl)phosphine **83o** (36.8 mg, 0.100 μmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (39.1 mg, 0.100 μmol) was added at room temperature. After being stirred for 15 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane/$CHCl_3$ (20:1, 3x2 mL) to give the product **81o** in 97% yield (64.1 mg, 0.097 mmol). Colorless crystals (from CH_3CN); Mp. 149-151°C; IR (ATR) ν = 2951, 2127, 1439, 1351, 1170, 1098, 834, 679, 577 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.17 (18H, d, J = 7.2 Hz), 1.25-1.34 (3H, m), 4.12 (2H, brs), 7.66 (4H, dt, J_{HP} = 11.5 Hz, J_{HH} = 7.8 Hz), 7.77 (2H, td, J_{HH} = 7.8 Hz, J_{HP} = 1.8 Hz), 7.91 (4H, dd, J_{HP} = 13.7 Hz, J_{HH} = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 11.0, 18.4, 32.9 (d, J_{CP} = 44.0 Hz), 56.8, 86.6 (d, J_{CP} = 159 Hz), 118.9 (br), 121.00 (q, J_{CF} = 327 Hz), 121.04 (q, J_{CF} = 327 Hz), 130.0 (d, J_{CP} = 13.5 Hz), 131.5 (d, J_{CP} = 13.7 Hz), 132.9 (d, J_{CP} = 10.7 Hz), 135.0 (d, J_{CP} = 3.1 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ = –15.9 (6F, s); ^{31}P NMR (162 Hz, $CDCl_3$) δ = 9.8; MS (ESI-TOF) *m*/*z* 681 $[M+H]^+$; HRMS calcd for $C_{27}H_{34}F_6O_4PS_2Si$ $[M+H]^+$, 681.1129; found, 681.1151.

Reaction of 2-fluoropyridinium salt 1d with phosphorus ylides 88:

1,1-Bis((trifluoromethyl)sulfonyl)-3-(triphenylphosphonio) propan-1-ide 82a. *n*BuLi (1.55m in *n*-hexane, 0.25 mL, 0.39 mmol) was added to a solution of methyltriphenylphosphonium bromide (146 mg, 0.410 mmol) in THF (2.0 mL) at 0ºC. The mixture was stirred for 30 min and then 2-fluoropyridinium salt **1d** (76.3 mg, 0.196 mmol) was added. Stirring was continued at RT for a further 2 h. Then, a saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction. After extraction with EtOAc (3x20 mL), the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography on neutral silica gel ($CHCl_3$/MeOH, 70:1) to give an impure material that mainly consisted of the desired product. This material was washed with *n*-hexane/Et_2O (1:1, 3x2 mL) to give the pure product **82a** in 62% yield (69.6 mg, 0.122 mmol). Colorless crystals (from EtOAc); m.p.>250 ºC (dec.); ^{1}H NMR (500 MHz, CD_3CN): δ = 2.78 (br s, 2H), 3.41 (br s, 2H), 7.55–7.66 (m, 6H), 7.66–7.75 (m, 6H), 7.80–7.87 ppm (m, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 23.2, 25.6 (d, J_{CP} = 43.0 Hz), 62.9, 118.0 (d, J_{CP} = 85.5 Hz), 121.2 (q, J_{CP} = 328 Hz), 130.7 (d, J_{CP} = 12.6 Hz), 133.2 (d, J_{CP} = 10.0 Hz), 135.4 ppm (d, J_{CP} = 3.1 Hz); ^{19}F NMR (376 Hz, CD_3CN): δ = –16.7 ppm (s, 6F); ^{31}P NMR (162 Hz, CD_3CN): δ = 21.3 ppm; IR (ATR): ν = 2924, 1346, 1190, 1160, 1112, 1206, 689, 578, 506 cm^{-1}; MS (ESI-TOF): *m/z* 591 $[M+Na]^+$; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{19}F_6NaO_4PS_2$: 591.0264 $[M+Na]^+$; found: 591.0267. CCDC-1833468 contains the supplementary crystallographic data for compound **82a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4-Ethoxy-4-oxo-1,1-bis((trifluoromethyl)sulfonyl)-3-(triphenylphosphonio)butan-1-ide 82b. To a solution of ethyl

(triphenylphosphoranylidene)acetate (78 mg, 224 μmol) in CH_3CN (1.0 mL), 2-fluoropyridinium salt **1d** (77.1 mg, 198 μmol) was added at room temperature. After being stirred for 2 h at the same temperature, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with a small amount of acetonitrile (*ca.* 0.5 mL) to give the product **82b** in 68% yield (86.4 mg, 135 μmol). Colorless crystals (from CH_3CN); Mp. 236-238 °C (decomp.); IR (ATR) ν = 2930, 1735, 1439, 1351, 1185, 1155, 1112, 1045, 689, 603, 503 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ = 1.04 (3H, t, *J* = 7.2 Hz), 2.87 (1H, br), 3.17 (1H, br), 3.91-4.09 (2H, m), 4.67 (1H, br), 7.62-7.73 (6H, m), 7.77-7.83 (6H, m), 7.84-7.89 (3H, m); ^{13}C NMR (125 MHz, CD_3CN) δ = 13.7, 30.5, 45.1 (d, J_{CP} = 44.9 Hz), 63.1, 63.9, 118.1 (d, J_{CP} = 86.3 Hz), 124.7 (q, J_{CF} = 327 Hz), 131.1 (d, J_{CP} = 12.8 Hz), 135.2 (d, J_{CP} = 10.3 Hz), 136.3 (d, J_{CP} = 2.8 Hz), 167.7; ^{19}F NMR (376 Hz, CD_3CN) δ = –16.7 (6F, s); ^{31}P NMR (162 Hz, CD_3CN) δ = 25.1; MS (ESI-TOF) *m*/*z* 663 $[M+Na]^+$; HRMS calcd for $C_{26}H_{23}F_6NaO_6PS_2$ $[M+Na]^+$, 663.0476; found, 663.0479. CCDC-1833467 contains the supplementary crystallographic data for compound **82b** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational Details: Structural optimisation calculation and the following frequency analysis were carried out by the Gaussian 09 program, revision D.01.[26] NBO and AIM analyses were carried out by using NBO 6.0 and AIMAll programs, respectively. [27,28] All calculations were done under M06-2x/6-311++G(d,p) level of theory. For NBO calculation, single point calculation with DFT optimised geometries at HF/def2-TZVPP[29] level of theory was also applied. The geometries are visualized by CYLview program.[30] NBOs were visualized by Jmol with Jmol-NBO Visualization Helper.[31]

IV.4. Notes and references

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X. CAPÍTULO 7

X.1. Transition Metal-Free Controlled Synthesis of Bis [(trifluoromethyl)sulfonyl]ethyl-decorated Heterocycles

Several heterocycles reacted with shelf-stable 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl] ethan-1-ide, a latent $Tf_2C{=}CH_2$ source, to give rise in a mild and controllable way to adducts via direct C–H bis[(trifluoromethyl)sulfonyl]ethylation reactions. This metal- and irradiation-free protocol is convenient. Besides, the volatile side-product 2-fluoropyridine can be smoothly eliminated under vacuum, which facilitates purification. The substrate scope survey discloses that exquisite chemo- and regioselectivities are achieved in a variety of heterocyclic systems. Of particular interest are the late-stage structural modification of known pharmaceuticals, such as the marketed drugs Phenazone (Antipyrine) and Edaravone, and the development of a water soluble fluorescent dye.

Org. Chem. Front. **2018**, *5,* 3163

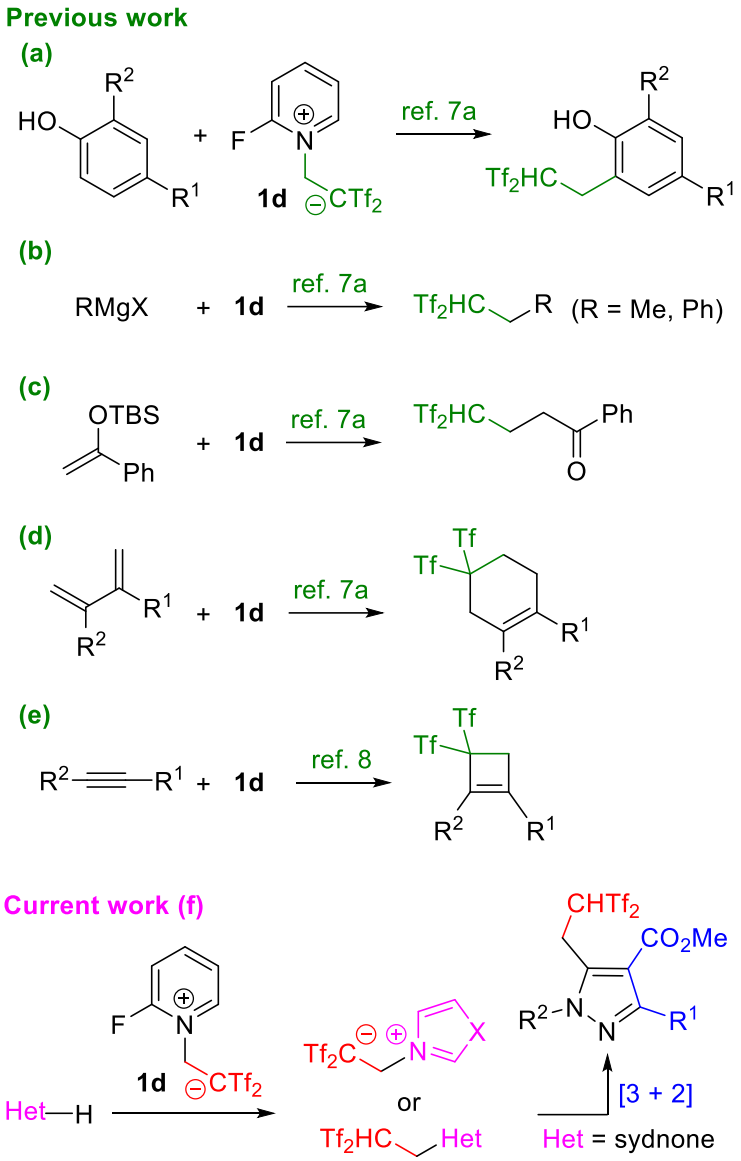
X.2. Article

X.2.1. Introduction

Heterocyclic scaffolds have fascinated chemists due to their widespread occurrence in bioactive compounds, functionalized dyes, and advanced materials. To improve the molecular functions of the heterocyclic compounds through regulating the physicochemical properties, incorporation of an additional functionality into the heterocyclic scaffolds is a common approach. In particular, fluorine-containing functionalities attract much attention because organic molecules having fluorinated functionalities display notable differences from their non-fluorinated counterparts in both their physicochemical and pharmacological properties.[1] A pivotal issue for efficient organic synthesis is the transformation of readily available precursors into target molecules in the fewest possible steps with a minimization of labour and waste. Demands for the efficient generation of diverse heterocyclic compounds bearing fluorinated substituents continue to stimulate the development of versatile synthetic strategies through late-stage structural modification. For example, fluoroalkyl heterocycles can be ideally prepared *via* direct C–H fluoroalkylation. However, the straightforward and selective fluoroalkylation of heterocycles is still a difficult task.[2,3] Besides, it should be taken into account that transition metal-catalyzed protocols raise safety concerns in medicinal and engineering applications due to the presence of metal impurities in the organic products.

In recent years, much attention has been paid to heterocycles bearing the trifluoromethylsulfonyl (trifyl) group (Tf = SO_2CF_3). The triflyl group is one of the strongest electron withdrawing substituents and it can endow the molecules with mild lipophilicity. Consequently, different strategies have been developed to prepare trifluoromethyl sulfones.[4] The electron withdrawing effect of the triflyl group also makes compounds bearing the *gem*-bis(triflyl)methyl group (Tf_2CH) strongly acidic. The acidity of such C–H acids is comparable to that of sulfuric acid;[5] therefore the Tf_2CH group has been already used as a key functionality in the development of highly effective acid catalysts.[4c,e,6] However, installing the Tf_2CH group into the heterocyclic scaffolds has not been reported. One of the serious drawbacks is

relatively strong basicity of nitrogen- containing heterocycles. As an effective methodology for Tf_2CH-functionalization, Yanai *et al.* reported the bis(triflyl) ethylation reaction of neutral nucleophiles such as phenols using highly electrophilic $Tf_2C{=}CH_2$, which can be *in situ* generated from Tf_2CH_2/formaldehyde or $Tf_2CHCH_2CHTf_2$.[4g] However, due to the strong acidity of Tf_2CH_2 and $Tf_2CHCH_2CHTf_2$, applying these conditions to basic or acid sensitive nucleophiles failed. Recently, Yanai and Matsumoto have developed 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** as an improved reagent.[7] Although this reagent is shelf-stable crystals, it rapidly releases $Tf_2C{=}CH_2$ in solutions accompanying the formation of 2-fluoropyridine. This achievement has allowed the effective bis(triflyl)ethylation reactions of not only phenols (Scheme X.1a)[7a] but also strongly basic or acid-sensitive species including Grignard reagents (Scheme X.1b),[7a] an enol silyl ether (Scheme X.1c),[7a] 1,3-dienes (Scheme X.1d)[7a] and alkynes (Scheme X.1e).[8] Given such background, we decided to pursue a transition metal-free methodology using **1d** for the direct incorporation of the Tf_2CHCH_2 group into several heterocyclic cores (Scheme X.1f).



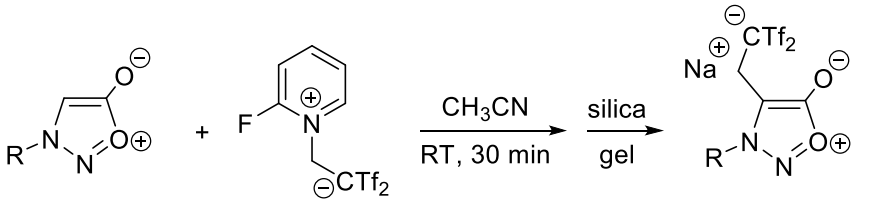
Scheme X.1. State-of-the-art and current study for the preparation of bis (triflyl)ethyl-molecules.

Our recent work revealed that attractive interactions between highly stabilized $[Tf_2CR]^-$ ions, the corresponding conjugate base of acid molecule Tf_2CHR, and countercations were negligibly weak.[9] Hence we hypothesized that installing the Tf_2CHCH_2 group on the heterocycles endows them with additional physicochemical properties such as water solubility; on the other hand, its influence on the molecular function originating from the heterocyclic structure is small. In this paper, we report the synthetic scope of the bis(triflyl)ethylation using 2-fluoropyridinium salt **1d** and its

applications to the late stage structural modification of commercial drugs and the development of a water-soluble heterocyclic fluorescent dye.

X.2.2. Results and discussion

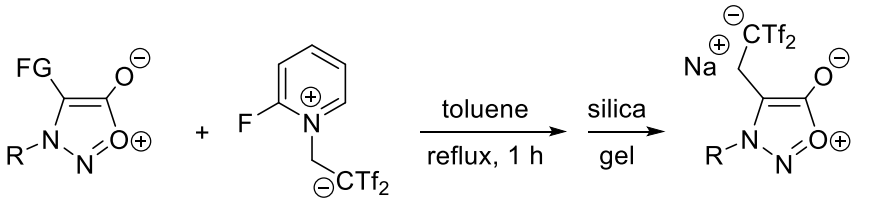
Recently, Alcaide and Almendros *et al.* have reported the [3+2] cycloaddition of azides with $Tf_2C{=}CH_2$ for the preparation of 4-triflyl-1,2,3-triazoles.[10] Bearing in mind this successful 1,3-dipolar cycloaddition reaction, we anticipated that the replacement of the azide moiety with a cyclic dipole, namely a sydnone, should deliver a direct route to trifyl-functionalized pyrazoles. Starting materials, sydnones 2a–j[11] and 2-fluoropyridinium salt **1d**[5] were prepared following literature procedures. To begin our research, we investigated the reaction of sydnone **89a** and $Tf_2C{=}CH_2$ **INT1** (generated *in situ* from zwitterion **1d**) in acetonitrile at room temperature. In the event, the highly nucleophilic C4 of sydnone[12] promotes the attack towards the 1,2-dipole $Tf_2C{=}CH_2$ to furnish the bis(trifyl)ethylation product **90a** (Scheme X.2), a novel type of sydnone derivative, in excellent yield.



89a R = Ph
89b R = 4-MeC_6H_4
89c R = 4-$MeOC_6H_4$
89d R = 4-$NO_2C_6H_4$
89e R = Me

1d

90a-Na (94%)
90b-Na (76%)
90c-Na (97%)
90d-Na (crude)
90e-Na (97%)



89f R = Ph, FG = I
89g R = 4-MeC_6H_4, FG = I
89h R = 4-$MeOC_6H_4$, FG = I
89i R = Ph, FG = COMe
89j R = Ph, FG = 4-MeC_6H_4

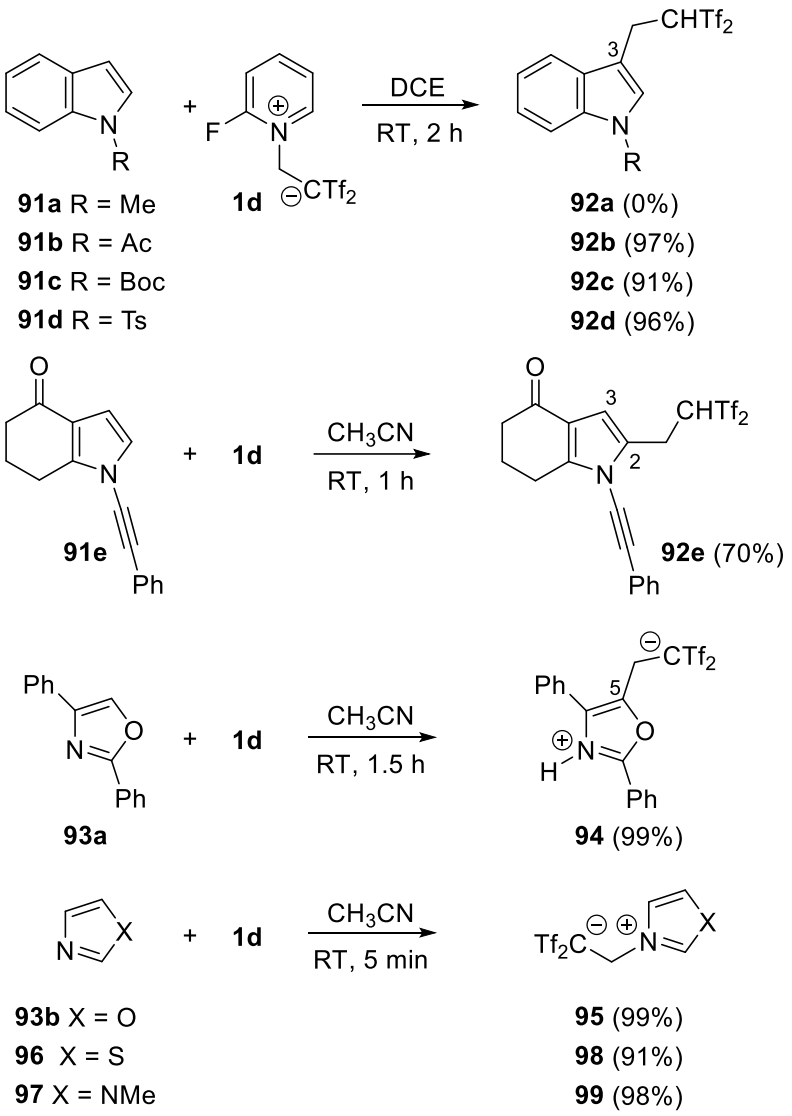
1d

90a-Na (72%)
90b-Na (87%)
90c-Na (76%)
90a-Na (90%)

Scheme X.2. Controlled synthesis of 4-bis(triflyl)ethyl-sydnones **90a–e**. The isolated yields were calculated as the Na^+ salt, because the corresponding Na^+ salts are the main component of the materials.

The [3+2] cycloaddition[13] of sydnone **89a** with $Tf_2C{=}CH_2$ was intended on more forcing conditions (toluene at reflux temperature) or through the use of Lewis acids (AgOTf, $In(OTf)_3$, ZnI_2), but resulted in the decomposition of the starting materials. C4-H sydnones **89b–e** reacted well with 2-fluoropyridinium salt **1d**, affording the corresponding bis (trifyl)alkylated sydnones **90b–e** in good yields (Scheme X.2). Nitro-derivative **90d** could not be isolated in pure form due to decomposition under chromatographic conditions, but can be used as a crude material for further reactions. Surprisingly, C4-functionalized sydnones **89f–i** (4-iodosydnones **89f–h** and 4-acetylsydnone **89i**) reacted with $Tf_2C{=}CH_2$ in boiling toluene to provide adducts of type **90** (Scheme X.2). C4-Tolyl sydnone **89j** did not react with reagent **1d**. Carbon acids **90a–e** dissociate the acidic hydrogen Tf_2CHR without difficulty. Consequently, their conjugate bases **90a–e-Na** were isolated as sodium salts after purification by flash column chromatography using silica gel as an adsorbent.[14,15]

With the transition metal- and irradiation-free conditions for bis(trifyl)ethylation of sydnones in hand, we next sought to establish a general bis(triflyl)ethylation of heteroarenes and enolizable heterocycles. Heteroarenes such as the 1*H*-indole, pyrrole, and oxazole nuclei readily participated and provided the required bis(triflyl)ethylated products using 1 equivalent of reagent **1d** (Scheme X.3).

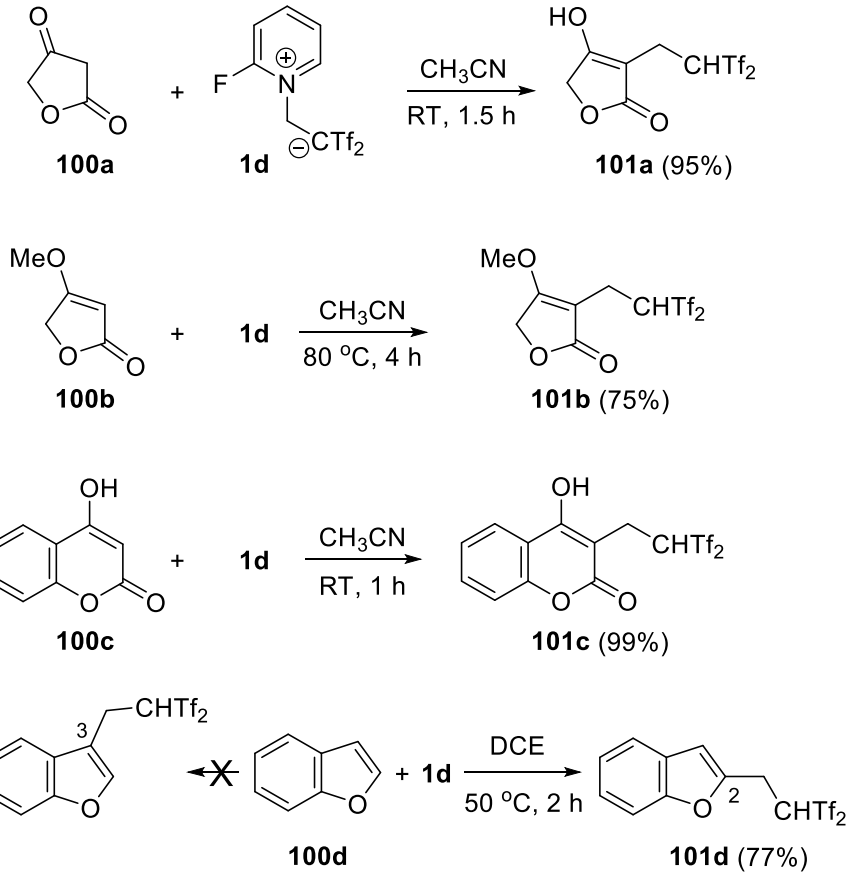


Scheme X.3. Controlled synthesis of (bis-triflyl)ethyl-heteroarenes **92b–e**, **94**, **95**, **98**, and **99**. DCE = 1,2-dichloroethane.

Although 1-methyl-1*H*-indole **91a** was too reactive and gave a complex reaction mixture, 1*H*-indoles bearing electron-withdrawing groups on the nitrogen gave bis (triflyl)ethylated products **92b–d** in a C3 selective manner. Pyrrole **91e** was a good example to survey chemo- and regioselectivity; under similar conditions, 2-substituted product **92e** was selectively obtained without formation of the [2+2] cycloadduct[6] as well as the 3-substituted product. In contrast to 2,4-diphenyloxazole **93a**, which gave 5-substituted product **94**, the reaction occurred at the nitrogen atom to give oxazolium salt **95** in the case of oxazole **93b** itself. Similar *N*-bis(triflyl)alkylation was observed in reactions of thiazole **96** and *N*-methylimidazole

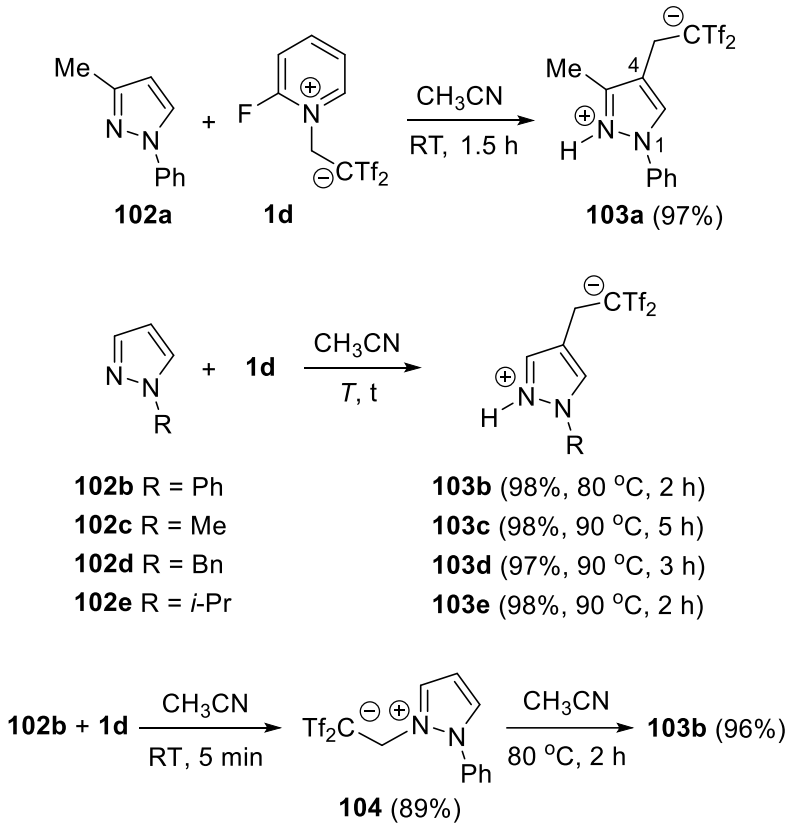
97. The structures of compounds **92e** and **94** were confirmed through their X-ray crystallographic studies.[16] Crystallographic structures of compounds **95** and **99** are available in the literature.[4b]

The substrate scope was also explored by replacing the heteroaryl scaffold with an oxygen-containing heterocyclic core. Pleasingly, tetronic acid **100a**, methyl tetronate **100b**, 4-hydroxy-coumarin **100c**, and benzofuran **100d** provided the desired *C*-bis(triflyl)ethylated products **101a–d** in good or excellent yields with total selectivity (Scheme X.4). We succeeded in obtaining the X-ray crystallographic structure of **101c**.[16]



Scheme X.4. Controlled synthesis of bis(triflyl)ethyl-heterocycles **101a–d**.

Among fluorinated heteroarenes, 1*H*-pyrazoles bearing fluorine- containing groups display outstanding biological properties.[17,18] As demonstrated in Scheme X.5, the direct bis(triflyl)ethylation of the pyrazole nucleus selectively proceeded at the C4 position.

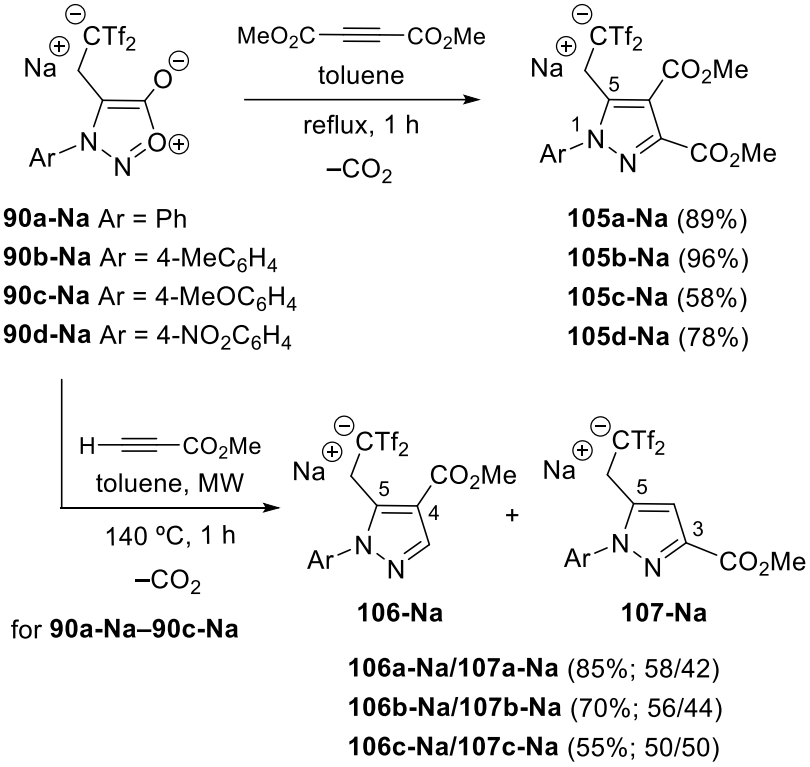


Scheme X.5. Controlled synthesis of bis(triflyl)ethyl-pyrazoliums **103a–e**.

For example, 1-phenyl-1*H*-pyrazoles **102a** and **102b** reacted under heating conditions with 2-fluoropyridinium salt **1** to provide 4-bis(triflyl)ethylated 1*H*-pyrazoles **103a** and **103b** in 97% and 98% yields, respectively. Note that the similar reaction at room temperature yielded the kinetically favorable *N*-alkylated product **104**, which can be easily converted into its counterpart **103b** in an irreversible fashion after gentle heating. All pyrazole-based adducts **103b–e** were isolated as *N*-protonated zwitterions, which were easily converted to the corresponding Na^+ salts by treatment with NaOMe. The structures of compounds **103a** and **104** were confirmed through the X-ray crystallographic study.[16] The observed C4-selectivity was consistent with the regioselectivity in the aromatic electrophilic substitution reactions of 1-substituted 1*H*-pyrazoles.

On the other hand, to the best of our knowledge, the preparation of pyrazoles bearing a triflyl-based moiety at the C5 position is underexplored.[18] Hence, with bis(triflyl)ethyl-sydnones **90** in hand, we planned to prepare 5-substituted pyrazoles through cycloaddition with alkynes and expulsion of CO_2. Mesoionic heterocycles **90**

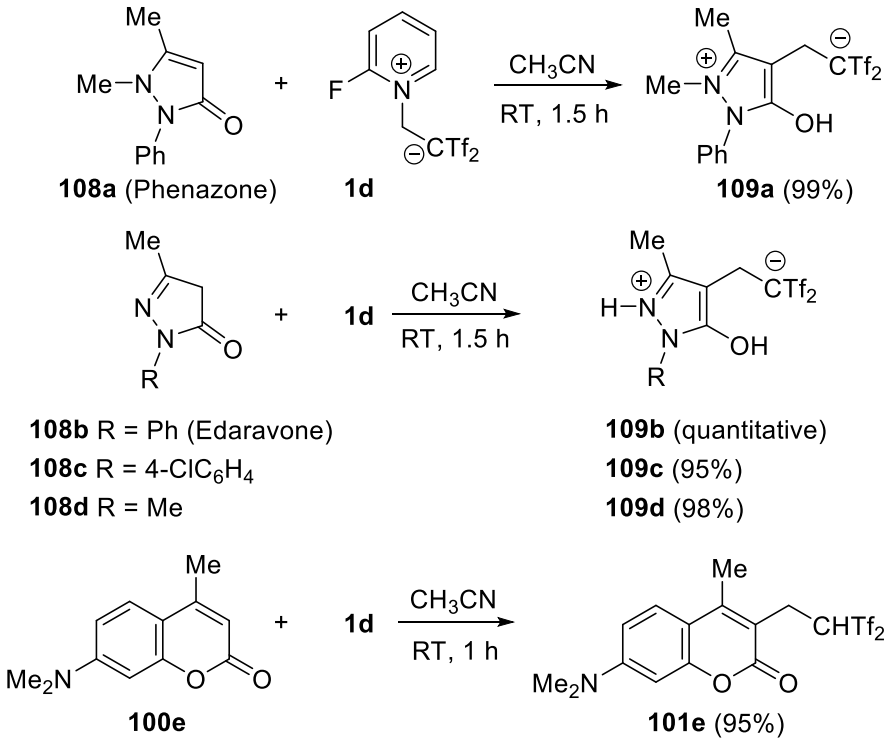
contain both an azomethine imine 1,3-dipole and a bis(triflyl)ethyl group as the anionic form. Indeed, functionalized sydnones **90** proved to be versatile synthons in installing the triflyl-based moiety to the C5 position of a 1*H*-pyrazole core *via* a simple thermal [3+2] cycloaddition reaction with alkynes. We were pleased to find that the desired 5-bis(triflyl)ethylated pyrazoles **105a–d** (as the corresponding Na^+ salts)[19] could be obtained in good isolated yields after silica gel chromatography when the reactions of functionalized sydnones **90** and dimethyl acetylenedicarboxylate were carried out in toluene at reflux temperature (Scheme X.6). The non-symmetric alkyne methyl propiolate afforded the desired cycloadducts in reasonable yields but as a mixture of regioisomers **106**/**107**. The formation of pyrazoles **106a–c**/**107a–c** required more forcing conditions (140°C, microwave heating).



Scheme X.6. Preparation of 5-bis(triflyl)ethyl-pyrazoles **105** and **106**/**107**.

In order to demonstrate applications of the present bis (triflyl)ethylation reaction, we finally addressed the following issues: (1) direct bis(triflyl)ethylation of marketed drugs and (2) possibility of the Tf_2CHCH_2 group as a water-soluble functionality. Of particular interest for the pharmaceutical industry in the discovery of more potent and efficient drugs is to make use of late-stage structural modification of known pharmaceuticals, without the necessity of starting the synthesis from the

beginning. Consequently, aiming to introduce the Tf_2CHCH_2 group into bioactive compounds, we selected marketed drugs such as Phenazone (Antipyrine) **108a** and Edaravone **108b** as pyrazolone nucleophiles (Scheme X.7).



Scheme X.7. Bis(triflyl)ethylation of biologically active pyrazolones including Phenazone **108a** and Edaravone **108b**, and blue fluorescent aminocoumarin **100e**.

Noticeably, these commercially available drugs were well tolerated under the reaction conditions with reagent **1d** to give bis(triflyl)ethylated molecules **109a** and **109b** in quantitative yields. Pyrazolones **108c** and **108d**, structurally related to Edaravone, also provided **109c** and **109d** in excellent yields and short reaction times. The structures of compounds **109a**, **109c**, and **109d** were confirmed through their X-ray crystallographic study.[20]

The improvement of water-solubility by incorporating the Tf_2CHCH_2 group was examined in 7-(dimethylamino)-4-methylcoumarin **100e**, which is a potent blue fluorescent dye [λ_{ex} 210 and 359 nm, λ_{em} 432 nm (in CH_3CN)]. This dye showed very poor solubility (<20 μg mL^{-1}) in 0.1 M phosphate buffers (pH 6.8 and 7.4) as well as water. Similarly to the case of 4-hydroxycoumarin **100c**, the bis(triflyl)ethylation of dye **100e** smoothly proceeded to give the Tf_2CHCH_2-decorated aminocoumarin **101e** in 95% yield (Scheme X.4 *vs*. 7). The thus obtained product did not show significant

changes of λ_{ex} (210 and 355 nm), λ_{em} (431 nm) and the shape of fluorescence emission spectra in CH_3CN (Figure X.1).

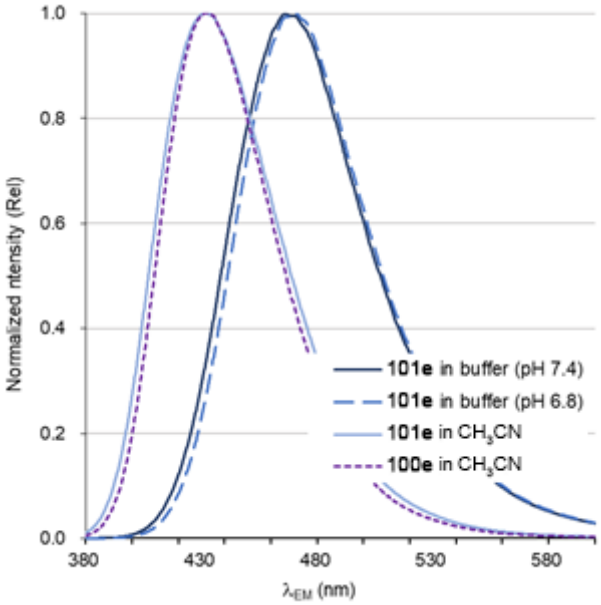


Figure X.1. Fluorescence emission spectra of Tf_2CHCH_2-decorated aminocoumarin dye **101e** and its counterpart **100e** at an excitation wavelength of 365 nm [5.0×10^{-1} mol L^{-1} solutions in 0.1 M phosphate buffers (pH 7.4 and 6.8) or CH_3CN].

However, its solubility in the aqueous media was improved and we successfully obtained the fluorescence emission spectra in the phosphate buffers (pH 7.4, λ_{em} = 470 nm; pH 6.8, λ_{em} = 471 nm). These fluorescence properties and improved solubility in aqueous solutions support our hypothesis that installation of the Tf_2CHCH_2 group on the heterocycle scaffold improves the water-solubility of lipophilic heterocyclic compounds; on the other hand, changes of the molecular function originated from the heterocyclic structure are negligible.

X.2.3. Conclusion

In summary, we have disclosed the metal- and irradiation-free C–H bis(triflyl)ethylation reactions of a variety of heterocycles with 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide. Bis(trifyl)ethylated products were obtained through a straightforward reaction between the heterocycle core and the *in situ* generated $Tf_2C{=}CH_2$, with the only side product generation of volatile 2-fluoropyridine. Satisfactory results in terms of chemo- and regioselectivity were obtained. Besides, the late-stage structural modifications of the marketed drugs Phenazone (Antipyrine) and Edaravone were easily achieved. The bis(triflyl)ethylation reaction also realized the development of a water-soluble aminocoumarin fluorescent dye.

X.3. Experimental Section

General methods: NMR spectra were recorded at 25 ºC on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance III Nanobay 400 MHz, or Bruker Avance-300 spectrometers. NMR spectra were recorded in $CDCl_3$, CD_3CN, CD_3COCD_3, or DMSO-d_6 solutions, except otherwise stated. Data are reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), and coupling constants (*J*, in Hz). Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm). Chemical shifts in ^{19}F NMR are given in ppm relative to (trifluoromethyl)benzene (–63.7 ppm). Chemical shifts in ^{23}Na are given in ppm relative to NaCl in D_2O (^{23}Na, 0.00 ppm). High resolution mass spectra were measured on a Waters Xevo G2-XS Tof mass spectrometer using electrospray ionization-time of flight (ESI-TOF) or were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. UV and Fluorescence spectra were recorded on a JASCO V-680 spectrometer and a Hitachi F-7100 spectrometer, respectively. Microwave irradiation was carried out in a Monowave 300 from Anton Paar GmbH. The reaction temperatures during microwave heating were measured with an internal infrared sensor. Column chromatography was carried out using silica gel 60, 0.04-0.06 mm, for flash chromatography (230-400 mesh ASTM) provided by Scharlau.

General Procedure for the Preparation of Bis(triflyl)ethyl-Sydnones 90a–e-Na. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.5 mmol) was added at room temperature to a solution of the appropriate sydnone **89** (0.5 mmol) in acetonitrile (for sydnones **89a−e**) or toluene (for sydnones **89f,i**) (5 mL). The reaction was stirred at room temperature for 30 min (from sydnones **89a−e**) or at reflux temperature for 1h (from sydnones **89f,i**) at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for compounds **90-Na** follow.

4-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate 90a-Na. From 50 mg (0.31 mmol) of sydnone **89a** and 120 mg (0.09 mmol) of 2-fluoropyridinium salt **1d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **90a-Na** (132 mg, 94% yield) as a yellow solid. Mp 245–247ºC; ^{1}H NMR (300 MHz, CD_3CN): δ = 7.72–7.55 (m, 5H), 3.56 (s, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ = 169.0, 135.0, 132.9, 130.7 (2C), 126.6 (2C), 122.1 (q, $J_{C–F}$ = 322.5 Hz, 2C), 109.7, 61.7, 22.6; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.60 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.39 (s, 1Na); IR ($CHCl_3$): ν = 2935, 1731, 1205 cm^{-1}; HRMS (ES): calcd for $C_{12}H_8F_6N_2NaO_6S_2$ $[M+Na]^+$: 476.9620; found: 476.9629.

4-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-3-(*p*-tolyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate 90b-Na. From 84 mg (0.28 mmol) of 4-iodosydnone **89g** and 109mg (0.28 mmol) of 2-fluoropyridinium salt **1d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **90b-Na** (116 mg, 87% yield) as a yellow solid. Mp 141–143ºC; ^{1}H NMR (300 MHz, CD_3CN): δ = 7.44 (m, 4H), 3.55 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ = 168.9, 143.6, 132.1, 131.1 (2C), 126.3 (2C), 122.1 (q, $J_{C–F}$ = 322.5 Hz, 2C), 109.4, 61.8, 22.7, 21.4; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.87 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.67 (s, 1Na); IR ($CHCl_3$): ν = 2934, 1732, 1207 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}F_6N_2NaO_6S_2$ $[M+Na]^+$: 490.9777; found: 490.9792.

4-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-3-(4-methoxyphenyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate 90c-Na. From 17 mg (0.09 mmol) of sydnone **89c** and 35 mg (0.09 mmol) of 2-fluoropyridinium salt **1d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **90c-Na** (27 mg, 97% yield) as a yellow solid. Mp 125–127ºC; ^{1}H NMR (300 MHz, CD_3CN): δ = 7.49 (AA'XX', 2H), 7.12 (AAXX', 2H), 3.87 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ = 169.2, 163.1, 128.0 (2C), 127.5, 122.1 (q, J_{C-F} = 329.6 Hz, 2C), 115.7 (2C), 109.8, 61.6, 56.6, 22.5; ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.91 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.65 (s, 1Na); IR ($CHCl_3$): ν = 2932, 1729, 1205 cm^{-1}; HRMS (ES): calcd for $C_{13}H_{10}F_6N_2NaO_7S_2$ [*M*+Na]$^+$: 506.9726; found: 506.9750.

4-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-3-methyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate 90e-Na. From 50 mg (0.50 mmol) of sydnone **89e** and 194 mg (0.50 mmol) of 2-fluoropyridinium salt **1d**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **90e-Na** (190 mg, 97% yield) as a colorless solid. Mp 72–74ºC; ^{1}H NMR (300 MHz, CD_3CN): δ = 4.06 (s, 3H), 3.59 (s, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ = 170.2, 122.0 (q, J_{C-F} = 324.8 Hz, 2CF_3), 108.8, 62.2, 38.8, 21.5; ^{19}F NMR (282 MHz, CD_3CN): δ = –81.30 (s, 6F); IR ($CHCl_3$): ν = 2938, 1735, 1208 cm^{-1}; HRMS (ES): calcd for $C_7H_6F_6N_2NaO_6S_2$ [*M*+Na]$^+$: 414.9464; found: 414.9478.

General Procedure for the Preparation of Compounds 92b-e and 94. 2-Fluoropyridinium salt **1d** (0.2 mmol) was added at room temperature to a solution of the appropriate heterocycles **91** and **93a** (0.2 mmol) in DCE (for compounds **91a−d**) or CH_3CN (for compounds **91e** and **93a**) (5.0 mL). The reaction was stirred at room temperature until disappearance of the starting heterocycles (TLC), and then the mixture was concentrated under reduced pressure. The purification details are described for each compound. Spectroscopic and analytical data for compounds **92** and **94** follow.

1-(3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-1*H*-indol-1-yl)ethan-1-one 92b. From 31.5 mg (0.198 mmol) of *N*-acetylindole **91b** and 77.2 mg (0.198 mmol) of 2-fluoropyridinium salt **1d**, compound **92b** (87.0 mg, 0.193 mmol, 97% yield) was obtained as a colorless solid after washing the crude material with hexane (4.0 mL x 3). Mp 120–121°C (from $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (brd, *J* = 8.2 Hz, 1H), 7.55–7.51 (m, 2H), 7.48–7.41 (m, 1H), 7.37 (td, *J* = 7.7, 1.0 Hz,1H), 5.09 (t, *J* = 5.8 Hz, 1H), 3.96 (d, *J* = 5.8 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 135.7, 128.1, 126.3, 126.2, 124.3, 119.2 (q, J_{CF} = 330 Hz), 117.5, 117.2, 112.8, 78.2, 23.9, 21.3; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –73.2 (s, 6F); IR (ATR): ν = 2907, 2891, 1697, 1454, 1384, 1203, 1099, 758, 698, 660, 639, 587, 552, 509, 481 cm^{-1}; MS (ESI-TOF) *m*/*z* 450 [M–H]$^-$; HRMS (ES): calcd for $C_{14}H_{10}F_6NO_5S_2$ [M–H]$^-$, 449.9905; found, 449.9897.

***tert*-Butyl 3-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1*H*-indole-1-carboxylate 92c**. From 42.6 mg (0.196 mmol) of *N*-(*tert*-butyloxy)carbonylindole **91c** and 78.0 mg (0.200 mmol) of 2-fluoropyridinium salt **1d**, compound **92c** (91.0 mg, 0.179 mmol, 91% yield) was obtained as a brown oil after flash chromatography on silica gel of the crude material (hexane/ethyl acetate = 5:1 as eluent), followed by acidification with 10% hydrochloric acid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (brd, *J* = 8.3 Hz, 1H,), 7.66 (s, 1H,), 7.53 (brd, *J* = 7.9 Hz,1H), 7.37-7.43 (m, 1H), 7.36−7.29(m, 1H), 5.10 (t, *J* = 5.8 Hz, 1H,), 3.95 (d, *J* = 5.8 Hz, 2H,), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 135.4, 128.2, 126.6, 125.3, 123.3, 119.2 (q, J_{CF} = 330 Hz), 117.6, 115.8, 111.2, 84.5, 78.4, 28.1, 21.3; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –73.4 (s, 6F); IR (ATR): ν = 2980, 2930, 1720, 1455, 1395, 1370, 1220, 1155, 1105, 745, 620 cm^{-1}; MS (ESI-TOF) *m*/*z* 508 [M–H]$^-$; HRMS calcd for $C_{17}H_{16}F_6NO_6S_2$ [M–H]$^-$, 508.0323; found, 508.0320.

3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-1-tosyl-1*H*-indole 92d. From 54.2 mg (0.200 mmol) of *N*-tosylindole **91d** and 78.8 mg (0.202 mmol) of 2-fluoropyridinium salt **1d**, compound **92d** (107.5 mg, 0.191 mmol, 96% yield) was obtained as colorless crystals after washing the crude material with a 5% solution of $CHCl_3$ in hexane. Mp 159−160°C (from $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H,) 7.66 (s, 1H), 7.49 (d, *J* = 7.8 Hz 1H), 7.43–7.37 (m, 1H,), 7.35-7.29 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 5.00 (t, *J* = 5.8 Hz 1H), 3.92 (d, *J* = 5.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 135.0, 134.8, 129.9, 128.4, 127.1, 126.9, 125.6, 124.0, 119.1 (q, J_{CF} = 330 Hz), 118.1, 114.2, 112.8, 78.2, 21.6, 21.3; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –73.5 (s, 6F); IR (ATR): ν = 2919, 1451, 1388, 1377, 1363, 1218, 1202, 1170, 1117, 1097, 973, 748, 666, 643, 570, 502 cm^{-1}; MS (ESI-TOF) *m*/*z* 562 $[M–H]^–$; HRMS calcd for $C_{19}H_{14}F_6NO_6S_3$ $[M–H]^–$, 561.9887; found, 561.9891. CCDC-1833410 contains the supplementary crystallographic data for compound **92d** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-(2,2-Bis((trifluoromethyl)sulfonylethyl)-1-phenylethynyl-1,5,6,7 tetrahydroindol-4-one 92e. From 30 mg (0.12 mmol) of 1-phenylethynyl-1,5,6,7-tetrahydroindol-4-one **91e** and 47 mg (0.12 mmol) of 2-fluoropyridinium salt **1d**, compound **92e** was obtained as a yellowish solid after washing the crude material with diclorometane/hexane. Mp 149–151°C (from $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 7.55 (m, 2H), 7.38 (m, 3H), 6.41 (s, 1H), 3.75 (s, 2H), 2.86 (t, *J* = 6.1 Hz, 2H), 2.34 (m, 2H), 2.11 (m, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 193.2, 146.6, 139.1, 132.2, 129.4, 129.3, 122.7, 122.5 (q, J_{CF} = 328.2 Hz), 121.8, 105.4, 78.9, 74.5, 63.3, 38.4, 26.3, 24.0, 22.5; ^{19}F NMR (282 Hz, CD_3COCD_3): δ = −79.9 (s, 6F); IR (CH_3COCH_3): ν = 2250, 1651, 1335, 1038, 1162 cm^{-1}; HRMS calcd for $C_{20}H_{16}F_6NO_5S_2^+$ $[M+H]^+$, 528.0369; found, 528.0382.

2-(2,4-Diphenyloxazol-3-ium-5-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 94. From 43.3 mg (0.196 mmol) of 2,4-diphenyloxazole **93a** and 78.4 mg (0.201 mmol) of 2-fluoropyridinium salt **1d**, compound **94** (99.3 mg, 0.193 mmol, 99% yield) was obtained as colorless crystals after washing the resulting solid with a 5% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 206–207°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.60–7.50 (m, 3H), 7.55–7.51 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7, 147.1, 134.9, 132.2, 130.6, 129.4, 128.8, 127.6, 127.4, 127.1, 125.7, 121.3 (q, J_{CF} = 329 Hz), 61.7, 25.2; ^{19}F NMR (376 Hz, DMSO-d_6): δ = –81.4 (s, 6F); IR (ATR): ν = 3170, 1657, 1606, 1577, 1340, 1318, 1176, 1090, 851, 629, 576, 509 cm^{-1}; MS (ESI-TOF) *m*/*z* 536 $[M+Na]^+$; HRMS calcd for $C_{19}H_{13}F_6NNaO_5S_2$ $[M+Na]^+$, 536.0037; found, 536.0038. Anal. Calcd for $C_{19}H_{13}F_6NO_5S_2$: C, 44.45; H, 2.55; N, 2.73. Found: C, 44.40; H, 2.80; N, 2.93. CCDC- 1832228 contains the supplementary crystallographic data for compound **94** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of Compounds 95, 98 and 99. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.20 mmol) was added at room temperature to a solution of the appropriate heterocycle **93b**, **96**, **97** (0.20 or 0.40 mmol) in CH_3CN (2.0 mL). The reaction was stirred for 5 min at room temperature, and then the mixture was concentrated under reduced pressure. The purification details are described for each compound. Spectroscopic and analytical data for compounds **95**, **98** and **99** follow.

2-(Oxazol-3-ium-3-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 95. From 26.5 µL (0.403 mmol) of oxazole **92b** and 77.0 mg (0.198 mmol) of 2-fluoropyridinium salt

1d, compound **95** (70.5 mg, 0.195 mmol, 99% yield) was obtained as colorless crystals after evaporation of the reaction mixture. The structure was confirmed by comparision of reported NMR spectroscopic data. ^{1}H NMR (400 MHz, CD_3CN) δ = 9.47 (1H, s), 8.25 (1H, s), 7.93 (1H, s), 5.25 (2H, brs); ^{13}C NMR (100 MHz, CD_3CN) δ = 154.5, 145.3, 122.3, 121.6 (q, J_{CF} = 325 Hz), 66.4, 51.1; ^{19}F NMR (376 Hz, CD_3CN) δ = –81.3 (s, 6F).

2-(Thiazol-3-ium-3-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 98. From 16.9 mg (0.199 mmol) of thiazole **96** and 77.1 mg of 2-fluoropyridinium salt **1d** (0.198 mmol), compound **98** (67.8 mg, 91% yield) was obtained as colorless crystals after washing the resulting solid with $CHCl_3$ (1.0 mL x 2). Due to the low stability in solution phase, we could not detect suitable peaks in the MS spectra. Mp. 138−140°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 9.72−9.67 (1H, m), 8.33 (1H, dd, *J* = 3.7, 1.1), 8.01 (1H, dd, *J* = 3.4, 2.7), 5.40 (2H, s); ^{13}C NMR (100 MHz, CD_3CN): δ = 158.4, 137.6, 127.0, 121.6 (q, J_{CF} = 325 Hz), 68.0, 56.2; ^{19}F NMR (376 Hz, CD_3CN): δ = –81.4 (s, 6F); IR (ATR): ν = 3119, 1557, 1342, 1321, 1174, 1140, 1109, 1057, 860, 728, 692, 637, 597, 565, 508 cm^{-1}; Anal. Calcd for $C_7H_5F_6NO_4S_3$: C, 22.28; H, 1.34; N, 3.71. Found: C, 22.13; H, 1.61; N, 3.84.

2-(1-Methyl-1*H*-imidazol-3-ium-3-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 99. From 16.8 mg (0.205 mmol) of 1-methylimidazole **97** and 77.4 mg (0.199 mmol) of 2-fluoropyridinium salt **1d**, compound **99** (73.2 mg, 0.196 mmol, 98% yield) was obtained as colorless crystals after evaporation of the reaction mixture. The structure was confirmed by comparision to reported NMR spectroscopic data. ^{1}H NMR (400 MHz, CD_3CN) δ = 8.51 (1H, s), 7.48 (1H, t, *J* = 1.8 Hz), 7.27 (1H, t, *J* = 1.8 Hz), 5.04 (2H, brs), 3.80 (3H, s); ^{13}C NMR (100 MHz, CD_3CN) δ = 136.4, 124.2, 122.8, 121.7 (q, J_{CF} = 326 Hz), 64.6, 50.1, 36.7; ^{19}F NMR (376 Hz, CD_3CN) δ = –81.4 (s, 6F).

General Procedure for the Preparation of Compounds 101a−d. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.20 mmol) was added at room temperature to a solution of the oxygen-containing heterocycle **93** (0.20 mmol) in CH_3CN (2.0 mL) (for compounds **100a−c**) or DCE (4.0 mL) (for compound **100d**). The reaction was stirred at room temperature (for compounds **100a** and **100c**), 50 °C (for compound **100d**) or 80 °C (for compound **100b**) until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. The purification details are described for each compound. Spectroscopic and analytical data for compounds **101a−d** follow.

3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-4-hydroxyfuran-2(5*H*)-one 101a. From 20.2 mg (0.202 mmol) of tetronic acid **100a** and 77.7 mg (0.200 mmol) of 2-fluoropyridinium salt **1d**, compound **101a** (74.2 mg, 0.189 mmol, 95% yield) was obtained as colorless crystals after washing the resulting solid with a 4% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 106−107°C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 9.67 (brs, 1H), 6.20 (brs,1H), 4.66 (s, 2H), 3.37 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ = 176.0, 175.0, 120.0 (q, J_{CF} = 329 Hz), 93.2, 74.3, 68.0, 19.9; ^{19}F NMR (376 Hz, CD_3CN): δ = –74.4 (s, 6F); IR (ATR): ν = 3059, 1717, 1656, 1627, 1391, 1235, 1202, 1114, 1097, 597, 497 cm^{-1}; MS (ESI-TOF) *m*/*z* 391 [M–H]$^-$; HRMS calcd for $C_8H_5F_6O_7S_2$ [M–H]$^-$, 390.9381; found, 390.9378. Anal. Calcd for $C_8H_6F_6O_7S_2$: C, 24.56; H, 1.39. Found: C, 24.63; H, 1.67.

3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-4-methoxyfuran-2(5*H*)-one 101b. From 23.2 mg (0.203 mmol) of methyl tetronate **100b** and 79.4 mg (0.204 mmol) of 2-fluoropyridinium salt **1d**, a mixture of compound **101b** (61.7 mg, 0.152 mmol, 75% yield) and 3-substituted isomer in a ratio of 7.4 : 1 was obtained as a colorless oil after purification by bulb-to-bulb distillation (180−200° C at 5 mmHg) using a Kugelrohr oven. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (t, *J* = 6.7 Hz, 1H), 4.79 (s, 2H), 4.03 (s. 3H), 3.40 (d, *J* = 6.7 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 175.5, 173.1, 119.1 (q, J_{CF} = 330 Hz), 94.4, 72.3, 65.6, 58.3, 19.4; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –74.0 (s, 6F); IR (film): ν = 2940, 1750, 1675, 1470, 1390, 1345, 1215, 1105, 1025, 700, 640 cm^{-1}; MS (ESI-TOF) *m*/*z* 405 $[M–H]^–$; HRMS calcd for $C_9H_7F_6O_7S_2$ $[M–H]^–$, 404.9537; found, 404.9536. Anal. Calcd for $C_9H_8F_6O_7S_2$: C, 26.11; H, 1.98. Found: C, 26.45; H, 2.22.

3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-4-hydroxy-2*H*-chromen-2-one 101c. From 31.6 mg (0.195 mmol) of 4-hydroxy-2*H*-chromen-2-one **100c** and 86.1 mg (0.221 mmol) of 2-fluoropyridinium salt **1d**, compound **101c** (87.9 mg, 0.193 mmol, 99% yield) was obtained as colorless crystals after washing the resulting solid with a 5% solution of Et_2O in hexane (1.0 mL x 3). Mp 287−289°C (from $CHCl_3$); ^1H NMR (400 MHz, CD_3CN): δ = 9.12 (brs, 1H), 7.89 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67−7.62 (m, 1H), 7.42-7.37(m, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 6.30 (br, 1H), 3.72 (s, 2H, s); ^{13}C NMR (100 MHz, CD_3CN): δ = 163.8, 163.3, 153.5, 134.0, 125,4, 124.2, 120.1 (q, J_{CF} = 329 Hz), 117.6, 116.1, 97.9, 74.9, 23.0; ^{19}F NMR (376 Hz, CD_3CN): δ = –74.5 (s, 6F); IR (ATR): ν = 2958, 2924, 1681, 1655, 1626, 1379, 1213, 1193, 1101, 1084, 644, 586, 477 cm^{-1}; MS (ESI-TOF) *m*/*z* 453 $[M–H]^–$; HRMS calcd for $C_{13}H_7F_6O_7S_2$ $[M–H]^–$, 452.9537; found, 452.9534. Anal. Calcd for $C_{13}H_8F_6O_7S_2$: C, 34.37; H, 1.77. Found: C, 34.51; H, 2.01. CCDC-1832226 contains the supplementary crystallographic data for compound **101c** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)benzofuran 101d. From 47.2 mg (0.400 mmol) of benzo[2,3]furan and 79.1 mg (0.203 mmol) of 2-fluoropyridinium salt **1d**, compound **101c** (64.4 mg, 0.157 mmol, 77% yield) was obtained as yellowish oil after bulb-to-bulb distillation (140-160°C at 5 mmHg) using a Kugelrohr oven. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58−7.54 (1H, m), 7.46 (1H, dd, *J* = 8.2, 0.8), 7.32 (1H, td, *J* = 9.6, 1.3), 7.29−7.23 (1H, m), 6.76 (1H, s), 5.43 (1H, t, *J* = 5.8 Hz), 4.00 (2H, d, *J* = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 147.4, 127.8, 125.1, 123.5, 121.4, 119.2 (q, J_{CF} = 330 Hz), 111.1, 107.4, 75.4, 24.9; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –73.8 (s, 6F); IR (ATR) ν = 2941, 1609, 1456, 1377, 1207, 1101, 948, 819, 748, 684, 632, 580, 516, 492, 464, 423 cm^{-1}; MS (ESI-TOF) *m*/*z* 409 $[M–H]^–$; HRMS calcd for $C_{12}H_7F_6O_5S_2$ $[M–H]^–$, 408.9639; found, 408.9641.

General Procedure for the Preparation of Compounds 103a−e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.20 mmol) was added at room temperature to a solution of pyrazole **102** (0.20 mmol) in CH_3CN (2.0 mL). The reaction was stirred at room temperature (for compounds **102a**) or 90 °C (in a sealed tube, for compound **103b−e**) until disappearance of the starting pyrazole (TLC), and then the mixture was concentrated under reduced pressure. The purification details are described for each compound. Spectroscopic and analytical data for compounds **101a−d** follow.

2-(3-Methyl-1-phenyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl) ethan-1-ide 103a. From 30.9 mg (0.195 mmol) of 3-methyl-1-phenyl-1*H*-pyrazole **102a** and 79.0 mg (0.203 mmol) of 2-fluoropyridinium salt **1d**, compound **103a** (76.2 mg, 97% yield) was obtained as colorless crystals after washing the crude material with a 5% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 185–187°C (from $CHCl_3$); ^1H NMR (400 MHz, CD_3CN): δ = 8.26 (s, 1H), 7.66–7.55 (m, 5H), 3.60 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 147.1, 135.6, 135.3, 131.3, 131.1, 125.3, 123.8, 122.2 (q, J_{CF} = 327 Hz), 64.8, 22.4, 9.8; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.8 (s, 6F); IR (ATR): ν = 3202, 3096, 1558, 1498, 1343, 1320, 1195, 1178, 1159, 1123, 1037, 873, 767, 616, 587, 567, 505 cm^{-1}; MS (ESI-TOF) *m*/*z* 473 $[M+Na]^+$; HRMS calcd for $C_{14}H_{12}F_6N_2NaO_4S_2$ $[M+Na]^+$, 473.0040; found, 473.0039. Anal. Calcd for $C_{14}H_{12}F_6N_2O_4S_2$: C, 37.34; H, 2.69; N, 6.22. Found: C, 37.34; H, 2.77; N, 6.37.

2-(1-Phenyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 103b. From 28.7 mg (0.199 mmol) of 1-phenylpyrazole **102b** and 76.4 mg (0.196 mmol) of 2-fluoropyridinium salt **1d**, compound **103b** (85.2 mg, 98% yield) was obtained as colorless crystals (from $CHCl_3$/hexane) after washing the crude material with a 5% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 146–148°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (s, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.54 (s, 1H), 7.42-7.49 (m, 2H), 7.25 (t, J = 7.3 Hz, 1H), 3.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 141.3, 140.2, 129.9, 126.1, 125.8, 124.9, 121.5 (q, J_{CF} = 330 Hz), 118.2, 64.8, 22.9; ^{19}F NMR (376 Hz, DMSO-d_6): δ = –81.3 (s, 6F); IR (ATR): ν = 3143, 1597, 1494, 1392, 1339, 1171, 1111, 1036, 759, 599, 580, 506 cm^{-1}; MS (ESI-TOF) *m*/*z* 459 $[M+Na]^+$; HRMS calcd for $C_{13}H_{10}F_6N_2NaO_4S_2$ $[M+Na]^+$, 458.9884; found, 458.9878. CCDC-1832225 contains the supplementary crystallographic data for compound **103b** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(1-Methyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 103c. From 16.7 mg (0.203 mmol) of 1-methylpyrazole **102c** and 77.8 mg (0.200 mmol) of 2-fluoropyridinium salt **1d**, compound **103c** (73.3 mg, 0.196 mmol, 98% yield) was obtained as colorless crystals after evaporation of the reaction mixture. Mp. 206–207°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 7.94 (s, 2H), 3.99 (s, 3H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ = 136.9, 133.8, 126.6, 122.2 (q, J_{CF} = 328 Hz), 64.9, 38.9, 23.3; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.8 (s, 6F); IR (ATR): ν = 3138, 1445, 1342, 1314, 1189, 1169, 1113, 1036, 836, 595, 583, 563, 507 cm^{-1}; MS (ESI-TOF) *m*/*z* 375 $[M+H]^+$; HRMS calcd for $C_8H_9F_6N_2O_4S_2$ $[M+H]^+$, 374.9908; found, 374.9902. Anal. Calcd for $C_8H_8F_6N_2O_4S_2$: C, 25.67; H, 2.15; N, 7.48. Found: C, 25.51; H, 2.33; N, 7.58.

2-(1-Benzyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 103d. From 32.2 mg (0.204 mmol) of 1-benzylpyrazole **102d** and 77.7 mg (0.200 mmol) of 2-fluoropyridinium salt **1d**, compound **103d** (87.2 mg, 0.194 mmol, 97% yield) was obtained as colorless crystals after washing the crude material with Et_2O (0.5 mL x 4). Mp. 69–70°C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 8.07 (s, 1H), 7.98 (s, 1H), 7.47–7.41 (m, 3H), 7.33–7.27 (m, 2H), 5.50 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ = 136.4, 134.8, 133.4, 130.3, 130.1, 129.1, 127.0, 122.2 (q, J_{CF} = 327 Hz), 65.0, 55.9, 23.3; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.8 (s, 6F); IR (ATR): ν = 3518, 3138, 3059, 2970, 1334, 1310, 1166, 1130, 1036, 873, 842, 734, 699, 588, 565, 507 cm^{-1}; MS (ESI-TOF) *m*/*z* 473 $[M+Na]^+$; HRMS calcd for $C_{14}H_{12}F_6N_2NaO_4S_2$ $[M+Na]^+$, 473.0040; found, 473.0034. Anal. Calcd for $C_{14}H_{12}F_6N_2O_4S_2$: C, 37.34; H, 2.69; N, 6.22. Found: C, 37.31; H, 2.96; N, 6.24.

2-(1-Isopropyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 103e. From 22.4 mg (0.203 mmol) of 1-isopropylpyrazole **102e** and 78.4 mg (0.201 mmol) of 2-fluoropyridinium salt **1d**, compound **103e** (79.4 mg, 0.197 mmol, 97% yield) was obtained as colorless crystals after washing the crude material with Et_2O (0.5 mL x 4). Mp. 173–174°C (from CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 8.02 (s, 1H), 7.98 (s, 1H), 4.76 (sept, J = 6.7 Hz, 1H), 3.58 (s, 2H), 1.53 (s, 2H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 134.0, 133.7, 126.5, 122.2 (q, J_{CF} = 327 Hz), 65.1, 56.8, 21.8; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.9 (s, 6F); IR (ATR): ν = 3201, 3147, 1331, 1309, 1183, 1168, 1117, 1039, 883, 837, 726, 652, 596, 583, 565, 509 cm^{-1}; MS (ESI-TOF) *m*/*z* 425 $[M+Na]^+$; HRMS calcd for $C_{10}H_{12}F_6N_2NaO_4S_2$ $[M+Na]^+$, 425.0040; found, 425.0037. Anal. Calcd for $C_{10}H_{12}F_6N_2O_4S_2$: C, 29.85; H, 3.01; N, 6.96. Found: C, 29.74; H, 3.31; N, 7.07.

2-(1-Phenyl-1*H*-pyrazol-2-ium-2-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 104. To a solution of 1-phenylpyrazole **102e** (28.6 mg, 0.198 mmol) in CH_3CN (2.0 mL), 2-fluoropyridinium salt **1d** (76.4 mg, 0.196 mmol) was added. After being stirred for 5 min at room temperature, the reaction mixture was concentrated under reduced pressure. Thus

obtained solid materials were washed with Et_2O (0.5 mL x 4) to give the product **104** in 89% yield (75.9 mg, 0.174 mmol) as colorless crystals. This compound formed an equilibrium mixture with $Tf_2C{=}CH_2$/1-phenylpyrazole in several solvents including DMSO-d_6. Finally, the structure was confirmed by an X-ray crystallographic analysis. Mp. 120–121°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.75 (d, J = 1.3 Hz, 1H), 7.54–7.44 (m, 2H), 7.31 (t, J = 7.4 Hz, 1H), 6.57–6.53 (m, 1H), 4.15 (s, 1H), 4.08 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 141.2, 140.0, 129.8, 127.9, 126.4, 121.1 (q, J_{CF} = 328 Hz), 118.6, 108.1, 66.3, 58.4; ^{19}F NMR (376 Hz, DMSO-d_6): δ = –81.7 (s, 6F); IR (ATR): ν = 3138, 1501, 1445, 1379, 1351, 1173, 1135, 1100, 1062, 857, 768, 695, 597, 566, 509 cm^{-1}; MS (ESI-TOF) m/z 437 $[M+H]^+$; HRMS calcd for $C_{13}H_{11}F_6N_2O_4S_2$ $[M+H]^+$, 437.0064; found, 437.0056. Anal. Calcd for $C_{13}H_{10}F_6N_2O_4S_2$: C, 35.78; H, 2.31; N, 6.42. Found: C, 35.61; H, 2.54; N, 6.58. CCDC-1843015 contains the supplementary crystallographic data for compound **104** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conversion of Bis(triflyl)ethyl-Pyrazole 103b to the Corresponding Na^+ Salt 103b-Na. To a solution of NaOMe (5.57 mg, 0.103 mmol) in MeOH (2.0 mL), 43.0 mg (98.5 µmol) of bis(triflyl)ethyl-pyrazole **103b** was added. After being stirred at room temperature for 10 min, the reaction mixture was evaporated and solidified by addition of $CHCl_3$ (1 mL). The resulting solid material was washed with $CHCl_3$ (0.5 mL x 2) and dried under reduced pressure to give sodium 2-(1-phenyl-1*H*-pyrazol-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide **103b-Na** (40.6 mg, 88.6 µmol, 90% yield). Mp. >250°C (from MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ = 7.93 (s, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.58 (s, 1H), 7.48–7.40 (m, 2H), 7.26 (t, J = 7.5 Hz, 1H), 3.56 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ = 142.0, 141.1, 130.3, 126.7, 126.5, 126.0, 122.4 (q, J_{CF} = 328 Hz), 119.2, 65.6, 23.5; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.6 (s, 6F); IR (ATR): ν = 1600, 1501, 1403, 1343, 1313, 1198, 1174, 1114, 1091, 1040, 1009, 875, 755, 721, 610, 599, 576, 504 cm^{-1}; MS (ESI-TOF) m/z 435 $[M]^-$; HRMS calcd for $C_{13}H_9F_6N_2O_4S_2$ $[M]^-$, 434.9908; found, 434.9915.

General Procedure for the Preparation of Bis(triflyl)ethyl-Pyrazoles 105a–d-Na. A stirred solution of the corresponding bis(triflyl)ethyl-sydnone **90-Na** (0.1 mmol) and dimethyl acetylenedicarboxylate (3.7 mmol) in toluene (0.8 mL) was heated at reflux temperature until disappearance of the starting material (TLC, 1 h). The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with hexanes/ethyl acetate mixtures. Spectroscopic and analytical data for pure forms of compound **105-Na** follow.

Dimethyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate 105a-Na. From 16 mg (0.04 mmol) of Tf-sydnone **90a-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **105a-Na** (17 mg, 89% yield) as a colorless solid. Mp 141–142ºC; ^{1}H NMR (300 MHz, CD_3CN): δ = 7.51–7.42 (m, 5H), 3.96 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ = 164.8, 163.9, 146.1, 143.4, 139.9, 130.2, 130.0 (2C), 127.8 (2C), 122.5 (q, J_{C-F} = 328.0 Hz, 2C), 116.3, 63.8, 52.9, 52.5, 24.0; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.6 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.64 (s, 1Na); IR ($CHCl_3$): ν = 1579, 1455, 1207 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{14}F_6N_2NaO_8S_2$ $[M+Na]^+$: 574.9988; found: 575.0000.

Dimethyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-(*p*-tolyl)-1*H*-pyrazole-3,4-dicarboxylate 105b-Na. From 20 mg (0.04 mmol) of Tf-sydnone **90b-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **105b-Na** (23 mg, 96% yield) as a colorless solid. Mp 218–219ºC; ^{1}H NMR (500 MHz, CD_3CN): δ = 7.30 (s, 4H), 3.91 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125

MHz, CD_3CN): δ = 164.9, 164.0, 146.0, 143.3, 140.4, 137.4, 130.5 (2C), 127.6 (2C), 122.2 (q, J_{C-F} = 328.2 Hz, 2C), 116.2, 63.9, 52.9, 52.5, 24.2, 21.3; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.6 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.67 (s, 1Na); IR ($CHCl_3$): ν = 1577, 1456, 1205 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{16}F_6N_2NaO_8S_2$ [*M*+Na]$^+$: 589.0145; found: 589.0139.

Dimethyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3,4-dicarboxylate 105c-Na. From 20 mg (0.07 mmol) of Tf-sydnone **90c-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **105c-Na** (22 mg, 58% yield) as a colorless solid. Mp 168–169ºC; ^1H NMR (500 MHz, CD_3CN): δ = 7.34 (AA'XX', 2H), 7.00 (AAXX', 2H), 3.90 (s, 2H), 3.84 (s, 6H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 164.9, 164.0, 161.2, 146.2, 143.2, 132.9, 129.2 (2C), 122.2 (q, J_{C-F} = 328.0 Hz, 2C), 116.0, 115.0 (2C), 63.9, 56.3, 52.9, 52.4, 24.1; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.6 (s, 6F); ^{23}Na NMR (132 MHz, CD_3CN): δ = –7.65 (s, 1Na); IR ($CHCl_3$): ν = 1581, 1458, 1206 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{16}F_6N_2NaO_9S_2$ [*M*+Na]$^+$: 605.0094; found: 605.0064.

Dimethyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-(4-nitrophenyl)-1*H*-pyrazole-3,4-dicarboxylate 105d-Na. From 120 mg (0.24 mmol) of crude Tf-sydnone **90d-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **105d-Na** (112 mg, 78% yield) as a colorless solid. Mp 127–128ºC; ^1H NMR (300 MHz, CD_3CN): δ = 8.33 (AA'XX', 2H), 7.70 (AAXX', 2H), 4.03 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ = 164.6, 163.7, 149.1, 147.0, 144.7, 144.3, 129.0 (2C), 125.5 (2C), 122.1 (q, J_{C-F} = 327.9 Hz, 2C), 116.9, 63.8, 53.2, 52.7, 23.9; ^{19}F NMR (282 MHz, CD_3CN): δ = –80.6 (s, 6F); IR ($CHCl_3$): ν = 1577, 1454, 1203 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{13}F_6N_3NaO_{10}S_2$ [*M*+Na]$^+$: 619.9839; found: 619.9846.

General Procedure for the Preparation of Bis(triflyl)ethyl-pyrazoles 106a–c-Na/107a–c-Na. A stirred solution of the corresponding bis(triflyl)ethyl-sydnone **90-Na** (0.04 mmol) and methyl propiolate (1.8 mmol) in toluene (0.4 mL) was heated at 140 ºC under microwave irradiation until disappearance of the starting material (TLC, 1 h). The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with hexanes/ethyl acetate mixtures. Spectroscopic and analytical data for pure forms of compound **106-Na/107-Na** follow.

Methyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-phenyl-1*H*-pyrazole-3/4-carboxylates 106a-Na/107a-Na. From 16 mg (0.04 mmol) of Tf-sydnone **90a-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compounds **106a-Na/107a-Na** (19 mg, 85%; a ratio of regioisomers = 58:42) as a colorless solid. Mp 128–130ºC; ^1H NMR (700 MHz, CD_3CN): δ = 7.86 (s, 1H, M), 7.55–7.42 (m, 10H, M + m), 6.87 (s, 1H, m), 4.13 (s, 2H, M), 3.86 (s, 3H, m), 3.78 (s, 3H, M), 3.64 (s, 2H, m); ^{13}C NMR (175 MHz, CD_3CN): δ = 165.1 (CO, M), 164.0 (CO, m), 148.2 (C_5, m), 145.9 (C_5, M), 143.9 (C_3, m), 141.7 (C_3, M), 140.6 (C_{Ar}, M), 140.1 (C_{Ar}, m), 130.2 ($2CH_{Ar}$, m), 129.8 (CH_{Ar}, M), 129.7 ($2CH_{Ar}$, M), 129.6 ($2CH_{Ar}$, m), 127.7 ($2CH_{Ar}$, M), 126.8 (CH_{Ar}, m), 121.4 (q, 2C, J_{C-F} = 327.8 Hz, $2CF_3$, m), 121.2 (q, 2C, J_{C-F} = 328.6 Hz, $2CF_3$, M), 114.9 (C_4, M), 109.9 (C_4, m), 64.3 (C-Tf_2, M), 64.1 (C-Tf_2, m), 52.4 (CH_3, m), 51.6 (CH_3, M), 26.2 ($2CH_2$, M + m); ^{19}F NMR (282 MHz, CD_3CN): δ = –80.4 (s, 6F, M + m); IR ($CHCl_3$): ν = 1588, 1460, 1209 cm^{-1}; HRMS (ES): calcd for $C_{15}H_{12}F_6N_2NaO_6S_2$ [*M*+Na]$^+$: 516.9933; found: 516.9920.

Methyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-(*p*-tolyl)-1*H*-pyrazole-3/4-carboxylates 106b-Na/107b-Na. From 14 mg (0.03 mmol) of Tf-sydnone **90b-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compounds **106b-Na/107b-Na** (11 mg, 70%; a ratio of regioisomers = 56:44) as a colorless

solid. Mp 153–155ºC; ^{1}H NMR (700 MHz, CD_3CN): δ = 7.84 (s, 1H, M), 7.35–7.27 (m, 8H, M + m), 6.85 (s, 1H, m), 4.11 (s, 2H, M), 3.85 (s, 3H, m), 3.78 (s, 3H, M), 3.61 (s, 2H, m), 2.42 (s, 3H, m), 2.40 (s, 3H, M); ^{13}C NMR (175 MHz, CD_3CN): δ = 165.0 (M), 163.9 (m), 148.0 (m), 145.7 (M), 143.6 (m), 141.5 (M), 139.9 (M), 139.6 (m), 138.0 (m), 137.6 (M), 130.6 (2C, M), 130.2 (2C, m), 127.5 (2C, M), 126.5 (2C, m), 121.4 (q, 2C, J_{C-F} = 327.4 Hz, m), 121.2 (q, 2C, J_{C-F} = 328.3 Hz, M), 114.7 (M), 109.6 (m), 64.1 (m), 64.0 (M), 52.3 (m), 51.5 (M), 26.1 (2C, M + m), 21.1 (2C, M + m); ^{19}F NMR (282 MHz, CD_3CN): δ = –80.4 (s, 6F, M + m); IR ($CHCl_3$): ν = 1589, 1461, 1207 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{14}F_6N_2NaO_6S_2$ [*M*+Na]$^{+}$: 531.0090; found: 531.0115.

Methyl 5-(2,2-bis((trifluoromethyl)sulfonyl)ethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3/4-carboxylates 106c-Na/107c-Na. From 10 mg (0.03 mmol) of Tf-sydnone **90c-Na**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compounds **106c-Na/107c-Na** (9 mg, 55%; a ratio of regioisomers = 50:50) as a colorless solid. Mp 138–140ºC; ^{1}H NMR (700 MHz, CD_3CN): δ = 7.82 (s, 1H, M), 7.36–7.31 (m, 4H, m), 7.05–6.96 (m, 4H, M), 6.82 (s, 1H, m), 4.05 (s, 2H, M), 3.85 (s, 3H, m), 3.84 (s, 3H, M), 3.83 (s, 3H, M), 3.77 (s, 3H, m), 3.59 (s, 2H, m); ^{13}C NMR (175 MHz, CD_3CN): δ = 165.0 (M), 163.9 (m), 160.7 (2C, M + m), 148.0 (m), 145.9 (M), 143.6 (m), 141.4 (M), 133.6 (M), 133.1 (m), 129.1 (2C, M), 128.1 (2C, m), 122.3 (q, 2C, J_{C-F} = 327.0 Hz, m), 122.2 (q, 2C, J_{C-F} = 328.8 Hz, M), 115.2 (2C, M), 114.8 (2C, m), 114.7 (M), 109.5 (m), 64.3 (M), 64.2 (m), 56.3 (M), 56.2 (m), 52.2 (m), 51.5 (M), 26.1 (2C, M + m); ^{19}F NMR (282 MHz, CD_3CN): δ = –80.4 (s, 6F, M + m); IR ($CHCl_3$): ν = 1586, 1457, 1203 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{14}F_6N_2NaO_7S_2$ [*M*+Na]$^{+}$: 547.0039; found: 547.0049.

General Procedure for the Preparation of Compounds 109a–d and 101e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (0.20 mmol) was added at room temperature to a solution of heterocycles **108a–d** and **100e** (0.20 mmol) in CH_3CN (2.0 mL). The reaction was stirred at room temperature until disappearance of the starting heterocycles (TLC), and then the mixture was concentrated under reduced pressure. The purification details are described for each compound. Spectroscopic and analytical data for compounds **109a–d** and **101e** follow.

2-(5-Hydroxy-2,3-dimethyl-1-phenyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 109a. From 36.7 mg (0.195 mmol) of Phenazone **108a** and 77.1 mg (0.198 mmol) of 2-fluoropyridinium salt **1d**, compound **109a** (92.4 mg, 99% yield) was obtained as colorless crystals after washing the crude material with a 3% solution of $CHCl_3$ in hexane (1.0 mL x 3). Mp 81–83°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, CD_3CN): δ = 10.65 (br, 1H), 7.74–7.64 (m, 3H), 7.47–7.42 (m, 2H), 3.58 (s, 2H), 3.42 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 155.3, 148.3, 132.9, 131.3, 130.7, 129.5, 121.9 (q, J_{CF} = 327 Hz), 104.3, 64.3, 34.2, 21.1, 10.6; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.9 (s, 6F); IR (ATR): ν = 3034, 1572, 1503, 1339, 1170, 1118, 1065, 1004, 692, 611, 599, 580, 561, 504 cm^{-1}; MS (ESI-TOF) *m*/*z* 503 [M+Na]$^{+}$; HRMS calcd for $C_{15}H_{14}F_6N_2NaO_5S_2$ [M+Na]$^{+}$, 503.0146; found, 503.0145. Anal. Calcd for $C_{15}H_{14}F_6N_2O_5S_2$: C, 37.50; H, 2.94; N, 5.83. Found: C, 37.28; H, 2.96; N, 5.89. CCDC- 1832230 contains the supplementary crystallographic data for compound **109a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 109b. From 35.0 mg (0.201 mmol) of Edaravone **108b** and 79.0 mg (0.203 mmol) of 2-fluoropyridinium salt **1d**, compound **109b** (93.6 mg, 0.201 mmol, 99.9% yield) was obtained as colorless crystals after washing the the crude material with hexane (2.0 mL x 5). Mp 147–148°C (from $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN):

δ = 7.65–7.53 (m, 5H), 3.56 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 154.6, 147.1, 133.1, 131.0, 130.7, 125.1, 122.9 (q, J_{CF} = 327 Hz), 105.2, 64.0, 20.8, 10.3; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.9 (s, 6F); IR (ATR): ν = 3242, 3079, 1564, 1501, 1335, 1305, 1180, 1013, 881, 604, 587 cm^{-1}; MS (ESI-TOF) *m*/*z* 489 $[M+Na]^+$; HRMS calcd for $C_{14}H_{12}F_6N_2NaO_5S_2$ $[M+Na]^+$, 488.9990; found, 488.9987. Anal. Calcd for $C_{14}H_{12}F_6N_2O_5S_2$: C, 36.06; H, 2.59; N, 6.01. Found: C, 35.90; H, 2.74; N, 6.07.

2-(1-(4-Chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-2-ium-4-yl)-1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide 109c. From 41.4 mg (0.198 mmol) of 2-(4-chlorophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **108c** and 78.9 mg (0.203 mmol) of 2-fluoropyridinium salt **1d**, compound **109c** (94.2 mg, 0.188 mmol, 95% yield) was obtained as colorless crystals after washing the crude material with 10% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 175–177°C (from $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ = 7.64–7.60 (m, 2H), 7.58–7.53 (m, 2H), 3.55 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 155.0, 147.6, 136.5, 131.6, 130.9, 126.7, 121.9 (q, J_{CF} = 326 Hz), 105.6, 64.0, 20.8, 10.4; ^{19}F NMR (376 Hz, CD_3CN): δ = –80.9 (s, 6F); IR (ATR): ν = 3245, 3088, 1497, 1337, 1304, 1183, 1173, 1069, 1010, 880, 830, 604, 586, 566, 504 cm^{-1}; MS (ESI-TOF) *m*/*z* 523 $[M+Na]^+$; HRMS calcd for $C_{14}H_{11}ClF_6N_2NaO_5S_2$ $[M+Na]^+$, 522.9600; found, 522.9603. Anal. Calcd for $C_{14}H_{11}ClF_6N_2O_5S_2$: C, 33.58; H, 2.21; N, 5.59. Found: C, 33.62; H, 2.34; N, 5.79. CCDC-1832227 contains the supplementary crystallographic data for compound **109c** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

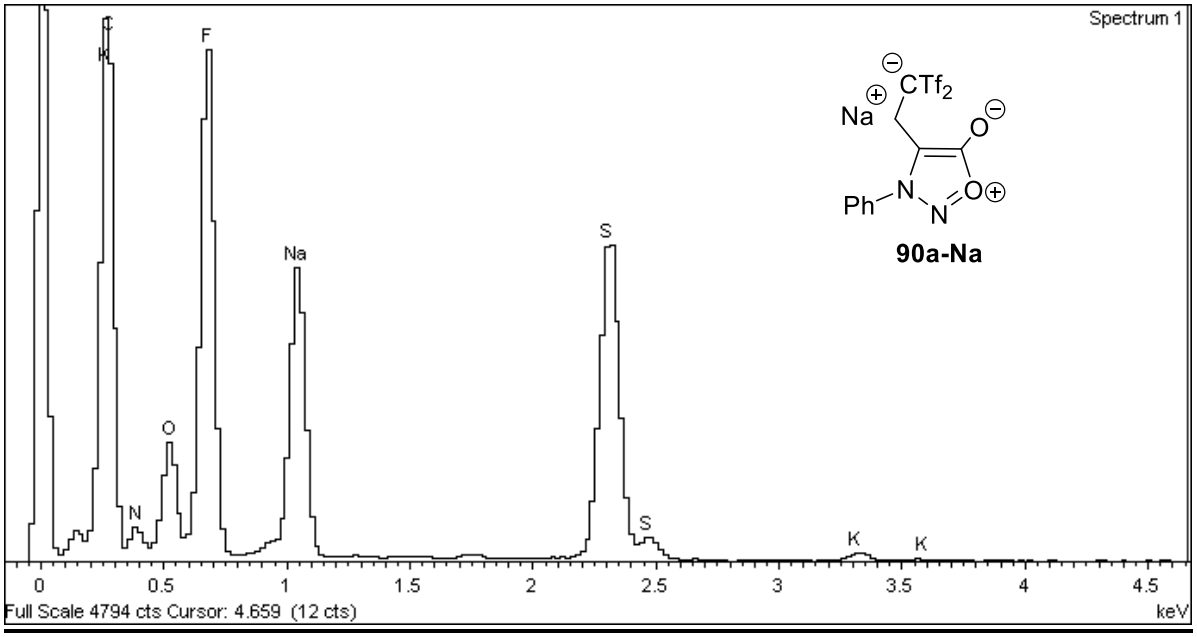
2-(5-Hydroxy-1,3-dimethyl-1*H*-pyrazol-2-ium-4-yl)-1,1 bis((trifluoromethyl)sulfonyl)ethan-1-ide 109d. From 21.9 mg (0.195 mmol) of 2,5-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one **108d** and 77.6 mg (0.199 mmol) of 2-fluoropyridinium salt **1d**, compound **109d** (77.1 mg, 0.191 mmol, 98% yield) was obtained as colorless crystals after washing the crude material with a 5% solution of $CHCl_3$ in hexane (1.0 mL x 2). Mp 168–169°C (from $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ = 3.64 (s, 3H); 3.46 (br, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ = 154.8, 144.7, 121.9 (q, J_{CF} = 326 Hz), 104.8, 64.3, 33.1, 20.7, 10.0; ^{19}F NMR (376 Hz, CD_3CN): δ = –81.0 (s, 6F); IR (ATR): ν = 3238, 3156, 1619, 1577, 1487, 1341, 1324, 1299, 1180, 1031, 926, 820, 595, 567, 505 cm^{-1}; MS (ESI-TOF) *m*/*z* 427 $[M+Na]^+$; HRMS calcd for $C_9H_{10}F_6N_2NaO_5S_2$ $[M+Na]^+$, 426.9833; found, 426.9830. Anal. Calcd for $C_9H_{10}F_6N_2O_5S_2$: C, 26.74; H, 2.49; N, 6.93. Found: C, 26.97; H, 2.54; N, 7.13. CCDC-1832229 contains the supplementary crystallographic data for compound **109d** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-(2,2-Bis((trifluoromethyl)sulfonyl)ethyl)-7-(dimethylamino)-4-methyl-2*H*-chromen-2-one 101e. From 39.9 mg (0.196 mmol) of 7-dimethylamino-4-methylcoumarin **13e** and 84.3 mg (0.217 mmol) of 2-fluoropyridinium salt **1d**, compound **101e** (92.6 mg, 0.187 mmol, 95% yield) was obtained as yellow crystals after washing the crude material with hexane (1.0 mL x 5). Mp. 137–139°C (from $CHCl_3$/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 6.35 (t, *J* = 6.9 Hz, 1H), 3.70 (d, *J* = 6.9 Hz, 2H), 3.08 (s, 6H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 154.4, 152.8, 126.3, 119.2 (q, J_{CF} = 330 Hz), 109.6, 109.5, 109.4, 73.9, 40.2, 25.4, 15.3; ^{19}F NMR (376 Hz, $CDCl_3$): δ = –74.2 (s, 6F); IR (ATR): ν = 2939, 2845, 1697, 1686, 1619, 1604, 1530, 1387, 1373, 1220, 1190, 1104, 798, 688, 639, 582, 497 cm^{-1}; MS (ESI-TOF) *m*/*z* 494 $[M–H]^–$; HRMS calcd for $C_{16}H_{14}F_6NO_6S_2$ $[M–H]^–$, 494.0167; found, 494.0172.

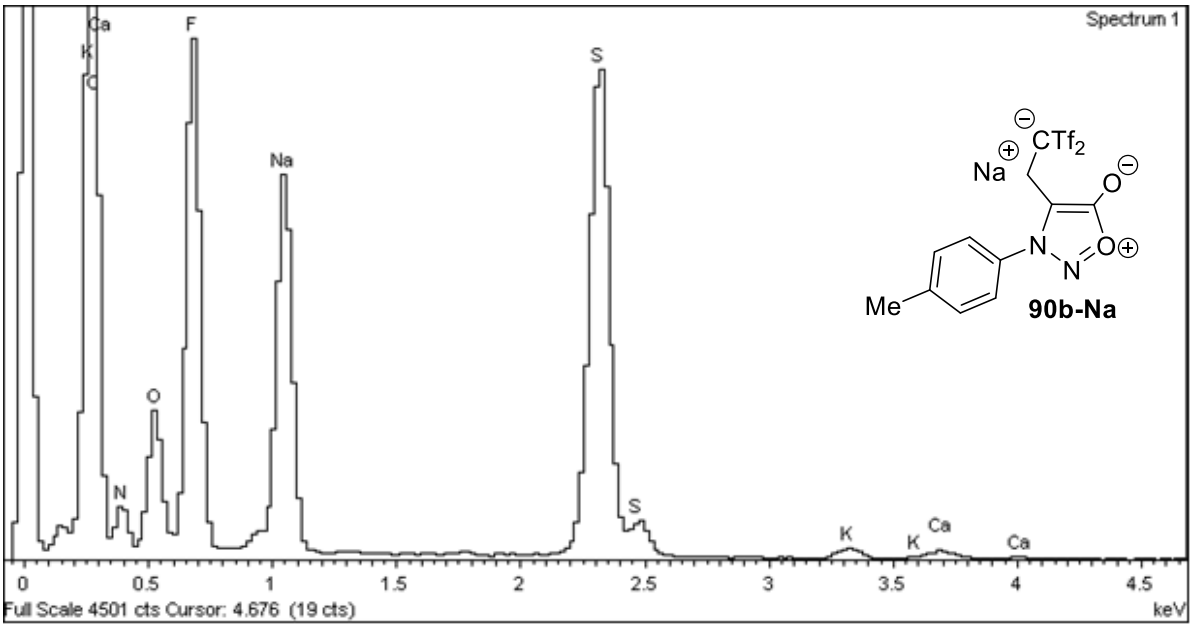
UV and Fluorescence Spectra

As initial solutions (4.0 x 10^{-4} mol L^{-1}), Tf_2CHCH_2-decorated aminocoumarin **101e** (4.95 mg, 10.0 μmol) was diluted to 25 mL with acetonitrile or 0.1 M phosphate buffers. To prepare 5.0 x 10^{-5} mol L^{-1} solutions for the UV/Vis spectroscopy, 1.25 mL of the initial solution was filled the same solvents to a volume of 10 mL. Likewise, 5.0 x 10^{-6} mol L^{-1} solutions used as fluorescence spectroscopy were prepared from 125 μL of the initial solutions. The UV, fluorescence excitation and emission spectra of aqueous solutions were obtained by measuring the samples three times. Due to low stability of **101e** in CH_3CN under UV irradiation conditions, the fluorescence spectra of **101e** in CH_3CN were obtained by measuring once. The fluorescence spectra were corrected by rhodamine B (in a range from 200 nm to 600 nm).

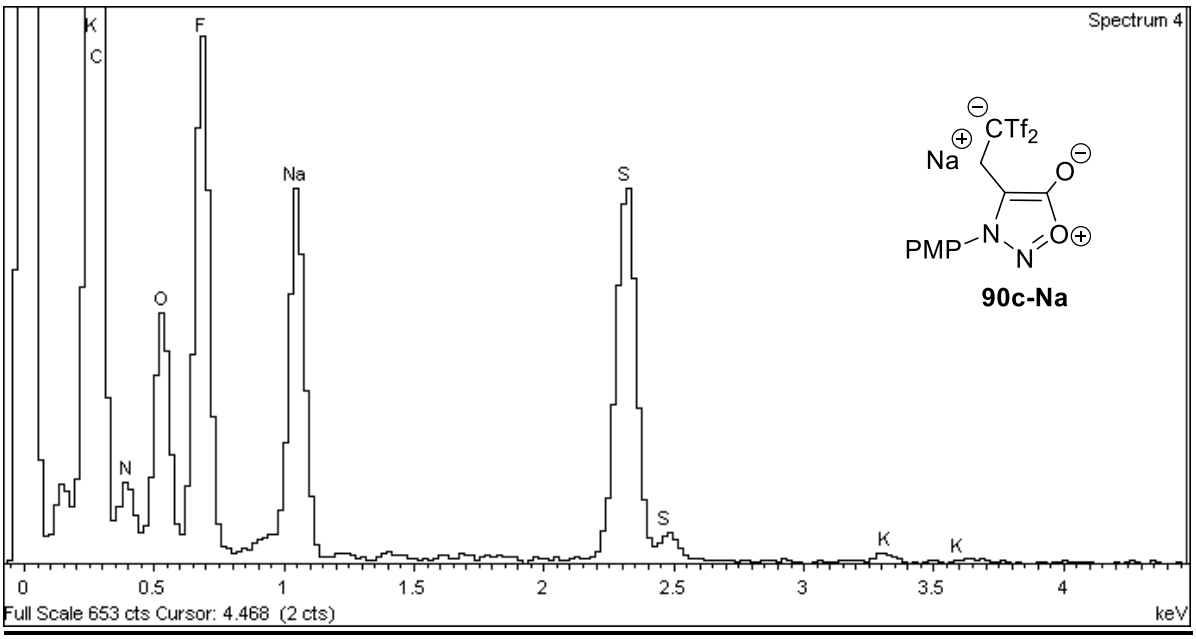
EDX Spectra



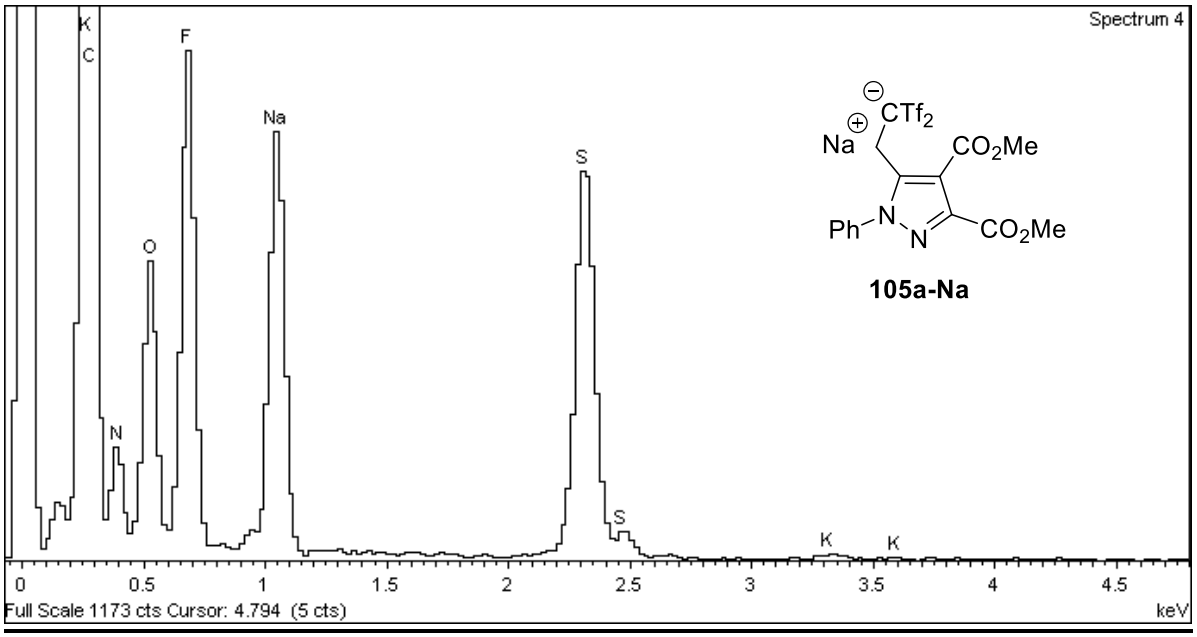
90a-Na EDX pattern. Copper cell.



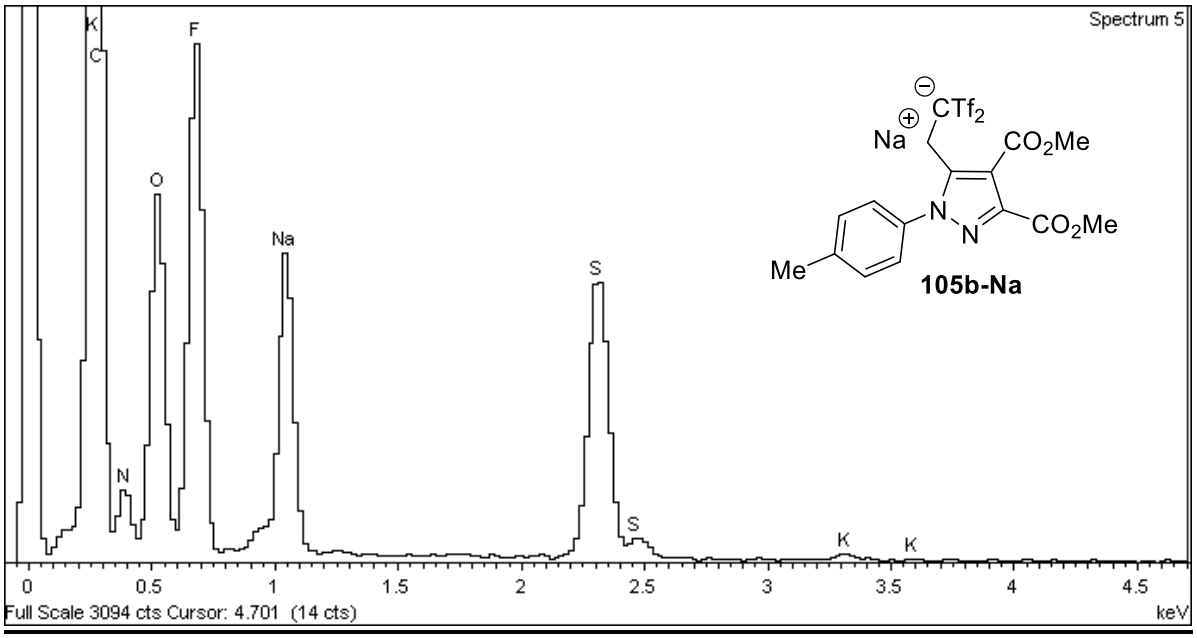
90b-Na EDX pattern. Copper cell.



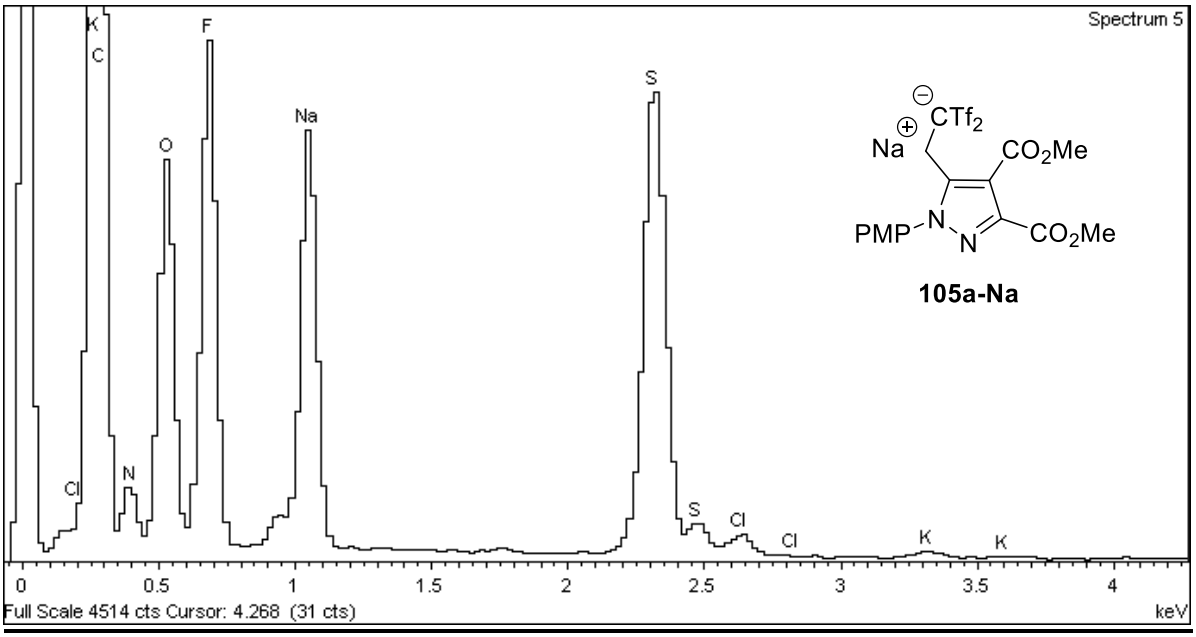
90c-Na EDX pattern. Copper cell.



105a-Na EDX pattern. Copper cell.



105b-Na EDX pattern. Copper cell.



105c-Na EDX pattern. Copper cell.

X.4. Notes and references

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15 The volatile side-product 2-fluoropyridine can be smoothly eliminated under vacuo, which facilitates chromatographic purification.

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20 CCDC 1832230, 1832227, and 1832229 contain the supplementary crystallographic data for compounds **109a**, **109c** and **109d** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

XI. CAPÍTULO 8

XI.1. Metal-free [3+2] Cycloaddition of Azides with $Tf_2C=CH_2$ for the Regioselective Preparation of Elusive 4-(trifluoromethylsulfonyl)-1,2,3-triazoles

1,2-Dipole $Tf_2C=CH_2$ is generated in situ and immediately reacts at room temperature with an azide to afford previously unknown 4-trifluoromethanesulfonyl 1,2,3-triazoles through a stepwise [3+2] cycloaddition reaction. Noteworthily, this mild and powerful uncatalyzed protocol is highly regio- and chemoselective.

Chem. Commun. **2015**, *51,* 6992

XI.2. Communication

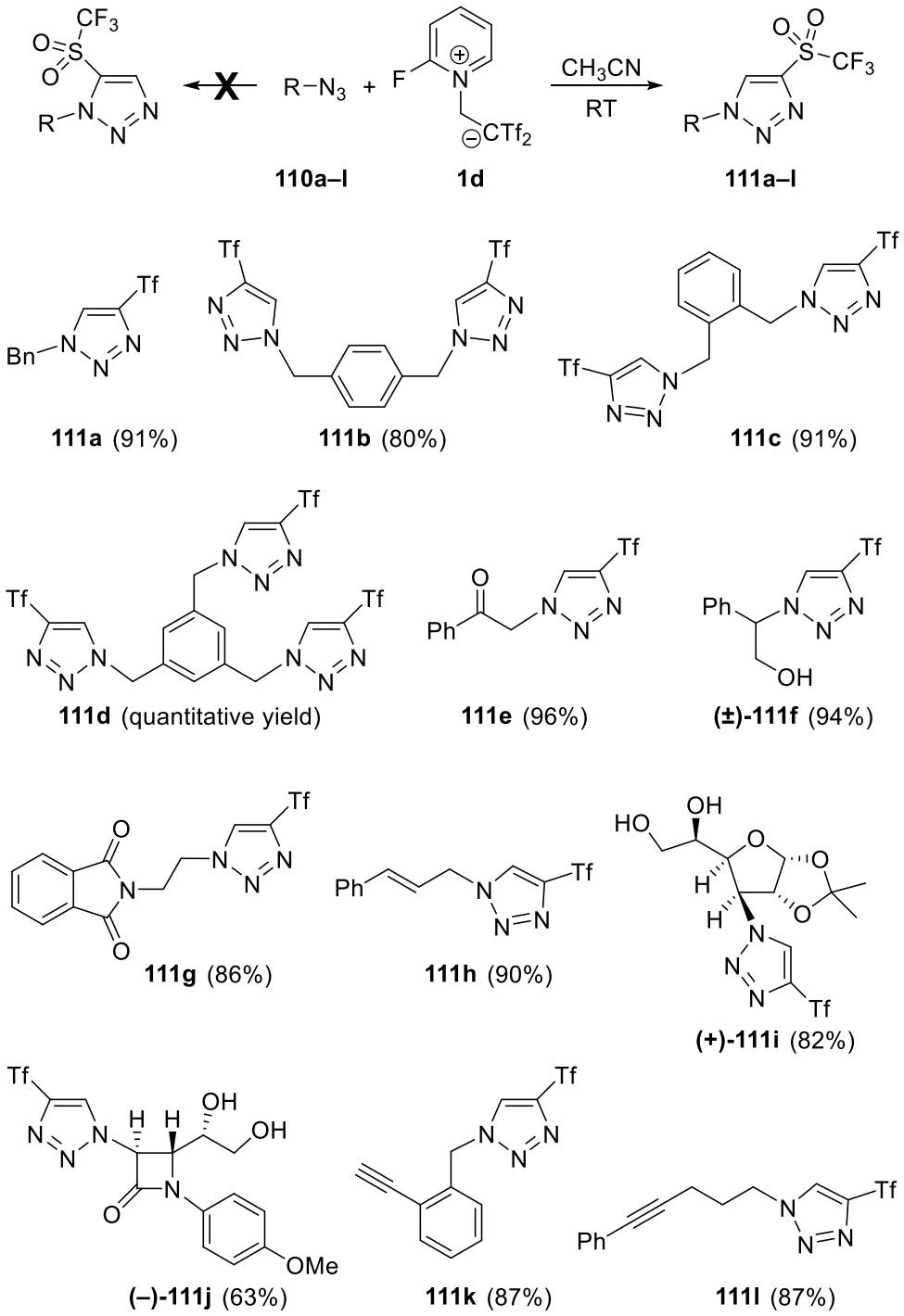
Substituted 1,2,3-triazoles are among the most important heterocyclic systems. They have found widespread applications in drug discovery, chemical biology, supramolecular chemistry and materials science.[1–9] 1,2,3-Triazoles are also useful precursors for the construction of more complex structures.[10–16] The classical route for the construction of the 1,2,3-triazole ring is achieved *via* the thermal Huisgen 1,3-dipolar cycloaddition of alkynes to azides.[17,18] This traditional protocol presents serious drawbacks because of the requirement for elevated temperatures and poor regioselectivity, resulting in a mixture of 1,4- and 1,5-regioisomers. Metal-catalyzed strategies have been merged recently for the regioselective formation of triazoles through alkyne–azide 1,3-dipolar cycloaddition (AAC). Of particular interest are the copper-,[19–22] ruthenium-,[23,24] silver-,[25] and gold-catalyzed[26] AACs. However, the widespread use of these metal-based triazole synthesis protocols for biological applications is precluded due to the cytotoxicity and eco-adverse effects of the heavy metals. Although several non-metal protocols have been described,[27–35] nowadays, there is an increasing interest in efficient metal-free strategies for the synthesis of the 1,2,3-triazole nucleus.

Fluoroorganic molecules exhibit peculiar biological activities because of their improved lipophilicity and metabolic stability.[36–39] The trifluoromethanesulfonyl moiety is particularly relevant due to its effectiveness for the modification of the chemical properties of organic compounds without changing molecular complexities.[40] *N*-Triflyl triazoles, whose reactivity can be further exploited,[41] are available taking advantage of the sulfonylation of *NH*-triazoles in the presence of triflic anhydride. Surprisingly, the preparation of the *C*-trifluoromethanesulfonylated triazole moiety counterpart has not been reported. The synthesis of carbonsubstituted triflyl triazoles may be precluded by their unavailability through the widely used AAC.

We envisioned that the highly polarized 1,1-bis(trifluoromethylsulfonyl)ethene **INT1** may be an effective reagent for the synthesis of *C*-triflyl triazoles through the reaction with azides. $Tf_2C{=}CH_2$ **INT1** reacts with alkynes and 1,3-dienes to give the corresponding gem-bis(triflyl)-cyclobutenes and gem-bis(triflyl)-cyclohexenes.[42,43]

Additionally, 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** has been identified as a stable precursor of **INT1** with the transfer of the Tf_2CH group to phenols.[44] In this context, we now wanted to explore whether the reaction of pyridinium salt **1d** with organic azides would open access to previously unknown *C*-triflyl 1,2,3-triazoles via a mild metal-free protocol.

The evaluation of the initial hypothesis was carried out using the readily available benzyl azide **110a**. In a first experiment with benzyl azide, we wanted to investigate whether or not the competing activation of the azide substrate **110a** was observed during its treatment with the reactive but sterically demanding species **INT1**. This was crucial as such a reactivity lacking the 1,3-dipolar cycloaddition pathway would provide undesired products. A strong solvent dependence was observed. Optimization of the solvent was limited by the insolubility of zwitterion **1d** in solvents such as dichloromethane, benzene and tetrahydrofuran, resulting in heterogeneous reaction conditions. Among the examined solvents, acetonitrile, dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were chosen to further optimize the reaction conditions because of the high solubility of precursor **1d** in these media. While DMSO and DMF were found to be unacceptable choices because of the overall low yields and the formation of byproducts, acetonitrile was the optimal solvent. Outstandingly, the reaction of benzyl azide **110a** with 1 equiv. of the zwitterionic reagent **1d** in acetonitrile at room temperature led to an almost quantitative yield of the desired *C*-triflyl triazole **111a** (Scheme XI.1). Notably, the cyclization reaction of **110a** in the presence of 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **1d** could be used in a large-scale reaction to afford **111a** in a similar yield. Spurred by the excellent results observed with benzyl azide, we examined the reactivity of a variety of azides under the above conditions. The results are presented in Scheme XI.1.

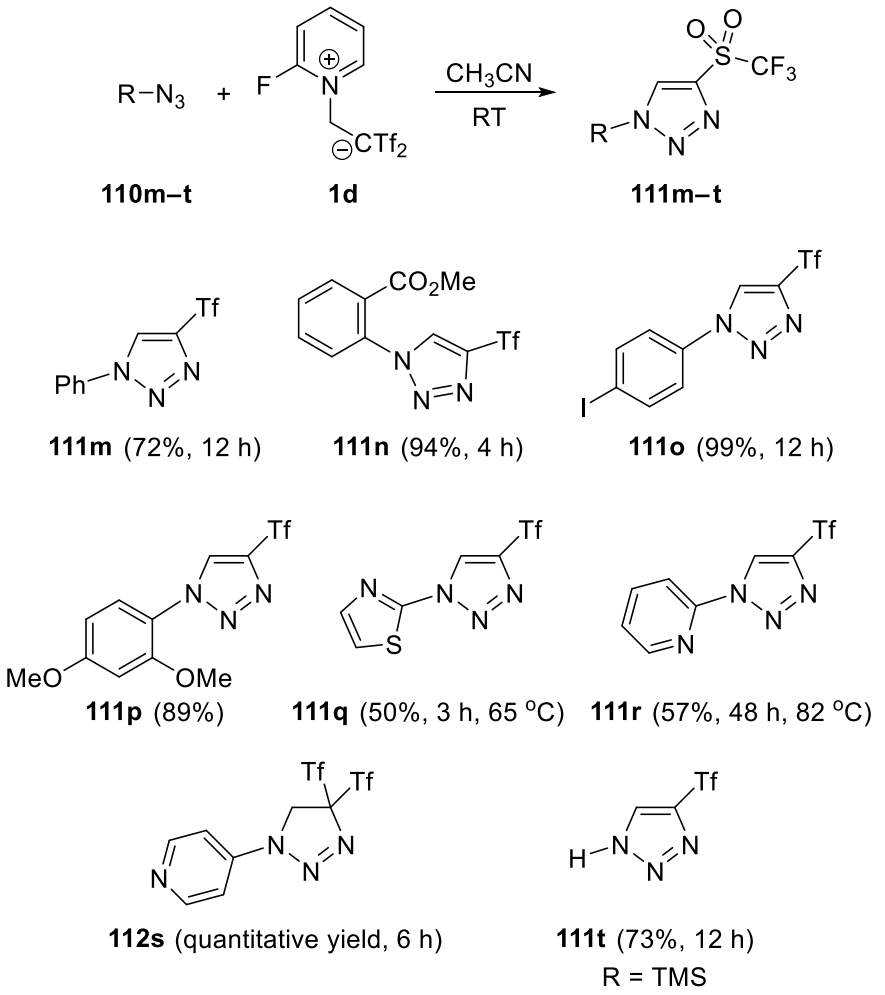


Scheme XI.1. Uncatalyzed synthesis of 1-alkyl-4-triflyl triazoles **111a–l** at room temperature from substituted alkyl azides **110a–l** and zwitterion **1d**.

Aliphatic azides **110a–l**, including allylic and phenacyl azides, instantaneously reacted to afford the corresponding *C*-triflyl triazoles **111a–l** in excellent yields.[45] The use of diazides **110b** and **110c** and triazide **110d** as substrates allowed the synthesis of bis(triazoles) **111b** and **111c** and tris(triazole) **111d**, respectively. The mildness of

the method did allow the use of enantiopure starting azides **110i** and **110j**. Reasonable yields of sugar- and β-lactam-linked triazoles **111i** and **111j** were observed without erosion of the stereochemical integrities (Scheme XI.1).[46] As is evident from the results shown in Scheme XI.1, total chemoselectivity was achieved because the reaction of the alkyne moiety was not observed in alkynyl azides **110k** and **110l**. The above results are of particular importance considering the fact that either intermolecular or intramolecular reactions of azides with alkynes usually afford triazoles.

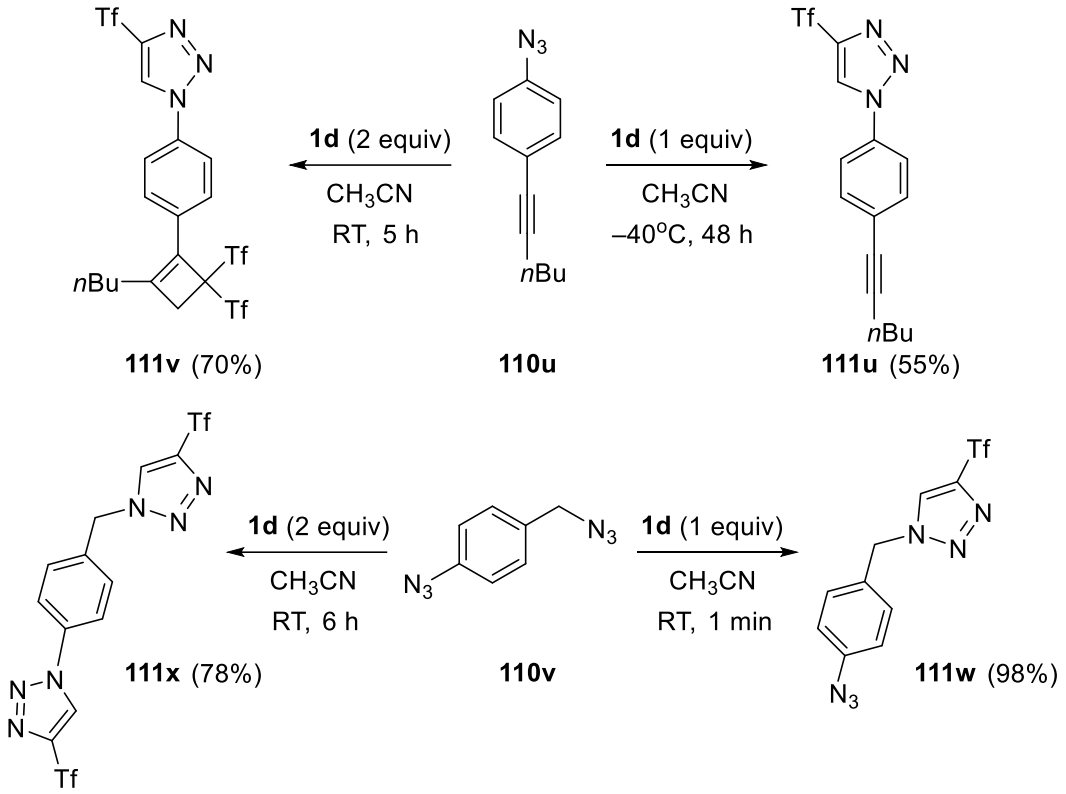
This metal-free method was applicable not only to aliphatic azides but also to aromatic ones; and the corresponding *C*-trifluoromethanesulfonylated triazoles **111m–r** were furnished in high yields undermild conditions (Scheme XI.2). While the reactions of alkyl azides **110a–l** were instantaneous, the reactions of their aromatic counterparts **110m–s** took several hours at room temperature. Interestingly, the formation of triazole **111p** from the electron-rich arene-containing azide **110p** was immediate. Heteroaromatic azides **110q** and **110r** also provided the desired 4-triflyl triazoles **111q** and **111r**, but after gentle heating (Scheme XI.2). Azide **110s** exclusively afforded 4-[4,4-bis(trifluoromethylsulfonyl)-4,5-dihydro-1H-1,2,3-triazol-1-yl]pyridine **112s**, but the aromatic adduct **111s** could not be obtained (Scheme XI.2). Upon the evaluation of the substrate scope for this transformation, we observed that trimethylsilyl (TMS) azide was also a suitable starting material. In the event, the formation of 4-triflyl triazole **111t** lacking the TMS group was observed (Scheme XI.2).



Scheme XI.2. Uncatalyzed synthesis of 1-aryl-4-triflyl triazoles **111m–r** at room temperature from substituted aryl azides **110m–r** and zwitterion **1d**.

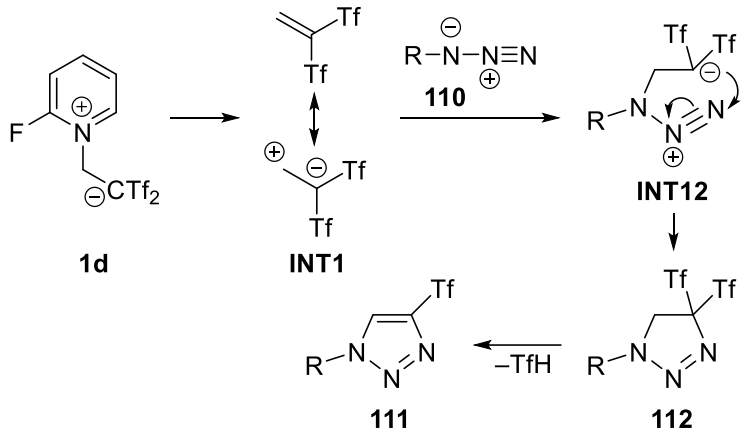
Under the optimized reaction conditions, the cyclobutenyl triazole **111v** was obtained in a reasonable yield from alkynyl azide **110u**. A temperature effect was observed by performing the reaction at low temperature (−40ºC), and the alkynyl triazole **111u** was exclusively formed (Scheme XI.3). The selective monofunctionalization of diazide **110v** bearing both aromatic and aliphatic azide moieties into 4-triflyl triazole **111w**, as well as the two-fold reaction to form bis(triazole) **111x** were also successfully developed (Scheme XI.3). Interestingly, the mildness of the protocol allows the chemocontrol and the discrimination in reactivity of the alkyl azide functionality (which underwent faster reaction rate) versus the corresponding reference aryl azide in **110v**. Noteworthily, the above-disclosed

chemoselectivity issues that are otherwise difficult to address using the AAC, have been easily resolved using our method.



Scheme XI.3. Controlled reactivity of alkynyl azide **110u** and diazide **110v**.

A conceivable mechanism for the formation of 4-trifluoromethanesulfonyl 1,2,3-triazoles **111** from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **1d** and organic azides **110** is shown in Scheme XI.4. It may initially involve the formation of 1,1-bis(trifluoromethylsulfonyl)ethene **INT1** from zwitterion **1d**. Next, the stepwise [3+2] cycloaddition reaction between azides **110** and the *in situ* generated 1,2-dipole **1**,[47] initially leading to the zwitterionic species **INT12** should take place. This addition product, zwitterion **INT12**, initiates a ring-closure reaction and produces the intermediate 1-substituted-4,4-bis(trifluoromethylsulfonyl)-4,5-dihydro-1H-1,2,3-triazoles **112**.[48] The formation of species **112** could trigger a rapid trifluoro(hydrosulfonyl)methane (TFH) elimination, thus leading to the final 4-triflyl 1,2,3-triazoles **111**. Possibly, the driving force of this process may be related to the gain in aromaticity associated with the triazole formation.



Scheme XI.4. Rationalization for the synthesis of 4-triflyl triazoles **111** from organic azides **110** and zwitterion **1d**.

In conclusion, 2-(2-fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl) sulfonyl]ethan-1-ide has been used as a precursor of the highly polarized 1,1-bis(trifluoromethylsulfonyl)ethene species $Tf_2C{=}CH_2$ in a metal-free stepwise [3+2] cycloaddition reaction of azides. This straightforward approach gives access, for the first time, to the previously elusive 4-trifluoromethanesulfonyl-1,2,3-triazoles from simple starting materials. Besides, the method is highly chemoselective and the reactions have been carried out at room temperature without the requirement of metals, bases or additives.

VIII.3. Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General experimental procedure for the 4-triflyl triazole formation. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1.0 mmol) was added at room temperature to a solution of the appropriate organic azide **110** (1.0 mmol) in acetonitrile (8.0 mL). After disappearance of the starting material (TLC) the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired heterocycle **111**. Spectroscopic and analytical data for 4-triflyl triazoles **111** follow.

4-Triflyl triazole 111a. From 40 mg (0.30 mmol) of azide **110a**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **111a** (79 mg, 91%) as a colorless solid; mp 81–83 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 5.67 (s, 2H, CH_2), 7.36 (m, 2H, 2CH^{Ar}), 7.45 (m, 3H, 3CH^{Ar}), 8.24 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.4 (C-Tf), 132.2 (C$^{Ar\text{-}q}$), 130.7 (CH-*Triazole*), 129.7 (CH^{Ar}), 129.6 (2CH^{Ar}), 128.6 (2CH^{Ar}), 119.3 (q, J_{CF} = 324.7 Hz, CF_3), 55.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.62 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1375, 1118 (O=S=O), 1222 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{10}H_8N_3O_2SF_3$ $[M]^+$: 291.0289; found: 291.0286.

Bis(4-triflyl triazole) 111b. From 20 mg (0.10 mmol) of azide **110b**, and after recrystallization (acetonitrile) gave compound **111b** (41 mg, 80%) as a colorless solid; mp 206–208 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, 25 ºC): δ = 5.80 (s, 4H, 2CH_2), 7.45 (s, 4H, 4CH^{Ar}), 9.71 (s, 2H, 2CH-*Triazole*); ^{13}C NMR (75 MHz, DMSO-d_6, 25 ºC): δ = 136.9 (2C-Tf), 134.9 (2C$^{Ar\text{-}q}$), 134.2 (2CH-*Triazole*), 129.0 (4CH^{Ar}), 119.0 (q, J_{CF} = 324.8 Hz, 2CF_3), 53.8 (2CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –79.14 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1376 (O=S=O), 1221 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{10}N_6O_4S_2F_6$ $[M]^+$: 504.0109; found: 504.0123.

Bis(4-triflyl triazole) 111c. From 20 mg (0.10 mmol) of azide **110c**, and after recrystallization (acetonitrile) gave compound **111c** (46 mg, 91%) as a colorless solid; mp 202–204 ºC; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 6.16 (s, 4H, 2CH_2), 7.46 (m, 4H, 4CH^{Ar}), 9.26 (s, 2H, 2CH-*Triazole*); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 ºC): δ = 139.3 (2C-Tf), 134.4 (2CH-*Triazole*), 134.0 (2C$^{Ar\text{-}q}$), 131.7 (2CH^{Ar}), 131.0 (2CH^{Ar}), 120.5 (q, J_{CF} = 323.8 Hz, 2CF_3), 52.7 (2CH_2); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.34 (s, 6F, 2CF_3); IR (acetone): ν = 1374, 1120 (O=S=O), 1215 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{10}N_6O_4S_2F_6$ $[M]^+$: 504.0109; found: 504.0086.

4-Triflyl triazole 111e. From 22 mg (0.13 mmol) of azide **110e**, and after flash chromatography of the residue using hexanes/dichloromethane (8:2→1:1) as eluent gave compound **111e** (42 mg, 96%) as a colorless solid; mp 144–146 ºC; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 6.44 (s, 2H, CH_2), 7.59 (t, 2H, J = 7.6 Hz, 2CH^{Ar}), 7.72 (t, 1H, J = 7.4 Hz, CH^{Ar}), 8.11 (d, 2H, J = 7.6 Hz, 2CH^{Ar}), 9.18 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz,

$(CD_3)_2CO$, 25 ºC): δ = 191.0 (C=O), 139.0 (C-Tf), 135.9 (CH-*Triazole*), 135.4 (CH^{Ar}), 134.9 ($C^{Ar\text{-}q}$), 130.0 ($2CH^{Ar}$), 129.2 ($2CH^{Ar}$), 120.5 (q, J_{CF} = 323.8 Hz, CF_3), 57.9 (CH_2); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.37 (s, 3F, CF_3); IR (acetone): ν = 1693 (C=O), 1380, 1122 (O=S=O), 1222 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{11}H_8N_3O_3SF_3$ $[M]^+$: 319.0238; found: 319.0239.

4-Triflyl triazole (±)-111f. From 20 mg (0.12 mmol) of azide (±)-**110f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound (±)-**111f** (36 mg, 94%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 2.64 (s, 1H, OH), 4.29 (dd, 1H, *J* = 12.3, 4.0 Hz, C*H*H), 4.59 (dd, 1H, *J* = 12.3, 7.7 Hz, CH*H*), 5.85 (dd, 1H, *J* = 7.7, 3.9 Hz, CH), 7.33 (m, 2H, $2CH^{Ar}$), 7.43 (m, 3H, $3CH^{Ar}$), 8.45 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.0 (C-Tf), 134.0 ($C^{Ar\text{-}q}$), 131.7 (CH-*Triazole*), 129.8 (CH^{Ar}), 129.6 ($2CH^{Ar}$), 127.3 ($2CH^{Ar}$), 119.3 (q, J_{CF} = 324.7 Hz, CF_3), 68.3 (CH), 64.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.52 (s, 3F, CF_3); IR ($CHCl_3$): ν = 3426 (OH), 1381, 1119 (O=S=O), 1217 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{11}H_{10}N_3O_3SF_3$ $[M]^+$: 321.0395; found: 321.0397.

4-Triflyl triazole 111g. From 20 mg (0.09 mmol) of azide **110g**, and after recrystallization (acetonitrile) gave compound **111g** (30 mg, 86%) as a colorless solid; mp 227–229 ºC; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 4.22 (m, 2H, CH_2), 4.95 (m, 2H, CH_2), 7.80 (m, 4H, $4CH^{Ar}$), 9.26 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 ºC): δ = 168.4 (2C=O), 139.2 (C-Tf), 135.4 ($2CH^{Ar}$), 134.8 (CH-*Triazole*), 132.9 ($2C^{Ar\text{-}q}$), 124.1 ($2CH^{Ar}$), 120.5 (q, J_{CF} = 323.8 Hz, CF_3), 50.9 (CH_2), 38.7 (CH_2); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.45 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1717 (C=O), 1373, 1134 (O=S=O), 1201 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_9N_4O_4SF_3$ $[M]^+$: 374.02966; found: 374.03092.

4-Triflyl triazole 111h. From 20 mg (0.16 mmol) of azide **110h**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **111h** (45 mg, 90%) as a colorless solid; mp 113–115 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 5.30 (dd, 2H, *J* = 7.0, 0.9 Hz, CH_2), 6.37 (dt, 1H, *J* = 15.7, 7.0 Hz, CH=C*H*-CH_2), 6.83 (d, 1H, *J* = 15.8 Hz, C*H*=CH-CH_2), 7.40 (m, 5H, $5CH^{Ar}$), 8.39 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.4 (C-Tf), 138.1 (CH=*C*H-CH_2), 134.6 ($C^{Ar\text{-}q}$), 130.5 (CH-*Triazole*), 129.2 (CH^{Ar}), 128.8 ($2CH^{Ar}$), 126.9 ($2CH^{Ar}$), 119.3 (q, J_{CF} = 324.7 Hz, CF_3), 119.0 (*C*H=CH-CH_2), 53.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.56 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1379, 1118 (O=S=O), 1215 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{10}N_3O_2SF_3$ $[M]^+$: 317.0446; found: 317.0450.

4-Triflyl triazole (+)-111i. From 34 mg (0.12 mmol) of azide (+)-**110i**, and after recrystallization (acetonitrile) gave compound (+)-**111i** (40 mg, 82%) as a colorless solid; mp 151–153 ºC; $[\alpha]_D$ = +5.1 (*c* 9.7, acetone); ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 1.33 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.08 (ddd, 1H, *J* = 9.0, 6.0, 5.0 Hz, CHOH), 3.80 (dd, 1H, *J* = 8.6, 4.9 Hz, C*H*H-OH), 3.94 (dd, 1H, *J* = 8.6, 6.1 Hz, CH*H*-OH), 4.42 (dd, 1H, *J* = 9.0, 4.0 Hz, CH), 5.24 (d, 1H, *J* = 3.6 Hz, CH), 5.47 (d, 1H, *J* = 4.0 Hz, CH), 6.22 (d, 1H, *J* = 3.6 Hz, CH), 9.14 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 ºC): δ = 138.7 (C-Tf), 135.9 (CH-*Triazole*), 120.5 (q, J_{CF} = 323.9 Hz, CF_3), 113.3 (C^q-*Acetonide*), 107.3 (CH), 84.4 (CH), 81.3 (CH), 73.4 (CHOH), 68.2 (CH), 68.1 (CH_2OH), 27.0 (CH_3), 26.4 (CH_3); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.37 (s, 3F, CF_3); IR (acetone): ν = 1383, 1028 (O=S=O), 1216 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_{16}N_3O_7SF_3$ $[M]^+$: 403.0661; found: 403.0681.

4-Triflyl triazole (–)-111j. From 30 mg (0.09 mmol) of azide (–)-**110j**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2→1:1) as eluent gave compound (–)-**111j** (25 mg, 63%) as a colorless solid; mp 115–117 ºC; $[\alpha]_D$ = –27.8 (*c* 3.5,

acetone); ^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 ºC): δ = 3.16 (s, 2H, 2OH), 3.77 (s, 3H, OCH_3), 4.00 (dd, 1H, *J* = 9.0, 5.9 Hz, C*H*H-OH), 4.24 (dd, 1H, *J* = 9.0, 6.8 Hz, CH*H*-OH), 4.73 (m, 1H, CH-OH), 4.93 (dd, 1H, *J* = 6.1, 2.4 Hz, CH-N), 6.15 (d, 1H, *J* = 2.4 Hz, CH-C=O), 6.94 (m, 2H, $2CH^{Ar}$), 7.56 (m, 2H, $2CH^{Ar}$), 9.44 (s, 1H, CH-*Triazole*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, 25 ºC): δ = 158.7 (C=O), 158.4 ($C^{Ar\text{-}q}$-OCH_3), 139.6 (C-Tf), 134.5 (CH-*Triazole*), 131.1 ($C^{Ar\text{-}q}$), 121.7 ($2CH^{Ar}$), 120.5 (q, J_{CF} = 323.8 Hz, CF_3), 115.1 ($2CH^{Ar}$), 76.5 (CHOH), 67.1 (CH-C=O), 66.4 (CH_2OH), 63.4 (CH-N), 55.9 (OCH_3); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.26 (s, 3F, CF_3); IR (acetone): ν = 3450 (OH), 1757 (C=O), 1381, 1102 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}N_4O_6SF_3$ $[M]^+$: 436.0664; found: 436.0664.

4-Triflyl triazole 111k. From 20 mg (0.12 mmol) of azide **110k**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **111k** (33 mg, 87%) as a colorless solid; mp 85–87 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.42 (s, 1H, C≡CH), 5.84 (s, 2H, CH_2), 7.44 (m, 3H, $3CH^{Ar}$), 7.63 (m, 1H, CH^{Ar}), 8.30 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.3 (C-Tf), 134.2 ($C^{Ar\text{-}q}$), 133.8 (CH^{Ar}), 130.8 (CH-*Triazole*), 130.1 (CH^{Ar}), 129.9 (CH^{Ar}), 129.8 (CH^{Ar}), 122.2 ($C^{Ar\text{-}q}$), 119.3 (q, J_{CF} = 324.7 Hz, CF_3), 83.7 (C≡*C*H), 80.2 (*C*≡CH), 53.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.56 (s, 3F, CF_3); IR ($CHCl_3$): ν = 3288 (≡C-H), 1381, 1119 (O=S=O), 1217 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{12}H_8N_3O_2SF_3$ $[M]^+$: 315.0289; found: 315.0285.

4-Triflyl triazole 111l. From 20 mg (0.10 mmol) of azide **110l**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→85:15) as eluent gave compound **111l** (30 mg, 87%) as a colorless solid; mp 99–101 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 2.31 (m, 2H, *J* = 6.8 Hz, CH_2), 2.53 (t, 2H, *J* = 6.6 Hz, CH_2), 4.74 (t, 2H, *J* = 6.9 Hz, CH_2), 7.33 (m, 3H, $3CH^{Ar}$), 7.41 (m, 2H, $2CH^{Ar}$), 8.40 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.2 (C-Tf), 131.6 ($2CH^{Ar}$), 131.1 (CH-*Triazole*), 128.4 ($2CH^{Ar}$), 128.3 (CH^{Ar}), 122.8 ($C^{Ar\text{-}q}$), 119.4 (q, J_{CF} = 324.8 Hz, CF_3), 86.2 (*C*≡C), 83.0 (C≡*C*), 50.3 (CH_2), 28.4 (CH_2), 16.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.58 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1381, 1120 (O=S=O), 1217 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{14}H_{12}N_3O_2SF_3$ $[M]^+$: 343.0602; found: 343.0604.

4-Triflyl triazole 111m. From 50 mg (0.42 mmol) of azide **110m**, and after flash chromatography of the residue using hexanes/ethyl acetate (90:10) as eluent gave compound **111m** (83 mg, 72%) as a colorless solid; mp 135–137 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.62 (m, 3H, $3CH^{Ar}$), 7.79 (m, 2H, $2CH^{Ar}$), 8.76 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 140.0 (C-Tf), 135.4 ($C^{Ar\text{-}q}$), 130.7 (CH^{Ar}), 130.3 ($2CH^{Ar}$), 128.8 (CH-*Triazole*), 121.1 ($2CH^{Ar}$), 119.4 (q, J_{CF} = 324.8 Hz, CF_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.38 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1382, 1111 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_9H_6N_3O_2SF_3$ $[M]^+$: 277.0133; found: 277.0136.

4-Triflyl triazole 111n. From 26 mg (0.14 mmol) of azide **110n**, and after flash chromatography of the residue using hexanes/dichloromethane (1:1) as eluent gave compound **111n** (46 mg, 94%) as a colorless solid; mp 119–121 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.73 (s, 3H, CH_3), 7.57 (dd, 1H, *J* = 7.5, 1.5 Hz, CH^{Ar}), 7.77 (m, 2H, $2CH^{Ar}$), 8.19 (dd, 3H, *J* = 7.2, 2.1 Hz, CH^{Ar}), 8.64 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 164.2 (C=O), 138.9 (C-Tf), 134.6 ($C^{Ar\text{-}q}$), 133.5 (CH^{Ar}), 133.4 (CH-*Triazole*), 132.1 (CH^{Ar}), 131.6 (CH^{Ar}), 127.5 (CH^{Ar}), 126.8 ($C^{Ar\text{-}q}$), 119.4 (q, J_{CF} = 324.8 Hz, CF_3), 52.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.59 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1725 (C=O), 1381, 1108 (O=S=O), 1216 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{11}H_8N_3O_4SF_3$ $[M]^+$: 335.0188; found: 335.0176.

4-Triflyl triazole 111o. From 23 mg (0.09 mmol) of azide **110o**, and after flash chromatography of the residue using hexanes/dichloromethane (8:2→1:1) as eluent gave compound **111o** (37 mg, 99%) as a colorless solid; mp 158–160 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.56 (m, 2H, $2CH^{Ar}$), 7.97 (m, 2H, $2CH^{Ar}$), 8.76 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 140.3 (C-Tf), 139.4 ($2CH^{Ar}$), 135.0 ($C^{Ar\text{-}q}$), 128.6 (CH-*Triazole*), 122.5 ($2CH^{Ar}$), 119.3 (q, J_{CF} = 324.8 Hz, CF_3), 96.2 ($C^{Ar\text{-}q}$-I); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.27 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1382, 1110 (O=S=O), 1217 (C–F) cm^{-1}; HRMS (ES): calcd for $C_9H_5N_3O_2SIF_3$ $[M]^+$: 402.9099; found: 402.9115.

4-Triflyl triazole 111p. From 25 mg (0.14 mmol) of azide **110p**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **111p** (42 mg, 89%) as a colorless solid; mp 103–105 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.65 (m, 2H, $2CH^{Ar}$), 7.77 (m, 1H, CH^{Ar}), 8.83 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.3 ($C^{Ar\text{-}q}$-OCH_3), 152.0 ($C^{Ar\text{-}q}$-OCH_3), 138.5 (C-Tf), 132.3 (CH-*Triazole*), 126.0 (CH^{Ar}), 119.5 (q, J_{CF} = 324.7 Hz, CF_3), 118.0 ($C^{Ar\text{-}q}$), 105.3 (CH^{Ar}), 99.5 (CH^{Ar}), 56.2 (OCH_3), 55.8 (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.62 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1380, 1106 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{11}H_{10}N_3O_4SF_3$ $[M]^+$: 337.0344; found: 337.0341.

4-Triflyl triazole 111q. From 20 mg (0.16 mmol) of azide **110q**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound **111q** (23 mg, 50%) as a colorless solid; mp 132–133 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.23 (d, 1H, J = 4.6 Hz, CH^{Ar}), 7.64 (d, 1H, J = 4.6 Hz, CH^{Ar}), 8.36 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 152.8 ($C^{Ar\text{-}q}$), 136.7 (C-Tf), 121.3 (CH-*Triazole*), 119.6 (q, J_{CF} = 325.2 Hz, CF_3), 118.4 (CH^{Ar}), 118.2 (CH^{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.32 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1364, 1101 (O=S=O), 1206 (C–F) cm^{-1}; HRMS (ES): calcd for $C_6H_3N_4O_2S_2F_3$ $[M]^+$: 283.9649; found: 283.9637.

4-Triflyl triazole 111r. From 27 mg (0.22 mmol) of azide **110r**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **111r** (35 mg, 57%) as a colorless solid; mp 102–104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.53 (ddd, 1H, J = 7.5, 4.9, 0.9 Hz, CH^{Ar}), 8.06 (td, 1H, J = 7.9, 1.8 Hz, CH^{Ar}), 8.28 (d, 1H, J = 8.2 Hz, CH^{Ar}), 8.59 (m, 1H, CH^{Ar}), 9.35 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 149.2 (CH^{Ar}), 147.6 (C-Tf), 139.9 (CH^{Ar}), 128.2 (CH-*Triazole*), 125.5 (CH^{Ar}), 119.4 (q, J_{CF} = 324.7 Hz, CF_3), 114.3 (CH^{Ar}), (*the signal for a $C^{Ar\text{-}q}$ was not detected because of the quadropole effect of the two nitrogen atoms bonded to it*); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.43 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1381, 1111 (O=S=O), 1213 (C–F) cm^{-1}; HRMS (ES): calcd for $C_8H_5N_4O_2SF_3$ $[M]^+$: 278.0085; found: 278.0086.

4-Triflyl triazole 111t. From 20 mg (0.17 mmol) of azide **110t**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **111t** (25 mg, 73%) as a colorless solid; mp 107–109 ºC; ^{1}H NMR (300 MHz, CD_3CN, 25 ºC): δ = 8.79 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, CD_3CN, 25 ºC): δ = 138.8 (C-Tf), 134.1 (CH-*Triazole*), 120.2 (q, J_{CF} = 323.6 Hz, CF_3); ^{19}F NMR (282 MHz, CD_3CN, 25 ºC): δ = –80.39 (s, 3F, CF_3); IR (acetone): ν = 1379, 1105 (O=S=O), 1214 (C–F) cm^{-1}; HRMS (ES): calcd for $C_3H_2N_3O_2SF_3$ $[M]^+$: 200.9820; found: 200.9827.

4-Triflyl triazole 111u. From 20 mg (0.10 mmol) of azide **110u**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3→9:1) as eluent gave compound **111u** (21 mg, 55%) as a colorless solid; mp 144–146 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.98 (t, 3H, J = 7.2 Hz, CH_3), 1.47 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.46 (t, 2H, J = 7.0 Hz, CH_2), 7.61 (d, 2H, J = 8.7 Hz, $2CH^{Ar}$), 7.72 (d, 2H, J = 8.7 Hz, $2CH^{Ar}$), 8.71

(s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 140.2 (C-Tf), 134.0 ($C^{Ar\text{-}q}$), 133.3 ($2CH^{Ar}$), 128.5 (CH-*Triazole*), 127.1 ($C^{Ar\text{-}q}$), 120.7 ($2CH^{Ar}$), 119.4 (q, J_{CF} = 324.8 Hz, CF_3), 94.3 (C≡*C*), 78.9 (*C*≡C), 30.5 (CH_2), 22.0 (CH_2), 19.1 (CH_2), 13.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.31 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1362, 1111 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{14}N_3O_2SF_3$ [*M*]$^+$: 357.0759; found: 357.0748.

4-Triflyl triazole 111v. From 20 mg (0.10 mmol) of azide **110u**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3→9:1) as eluent gave compound **111v** (45 mg, 70%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.97 (t, 3H, *J* = 7.2 Hz, CH_3), 1.46 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.63 (t, 2H, *J* = 7.6 Hz, CH_2), 3.43 (s, 2H, CH_2-*Cyclobutene*), 7.82 (d, 2H, *J* = 8.9 Hz, $2CH^{Ar}$), 7.88 (d, 2H, *J* = 8.9 Hz, $2CH^{Ar}$), 8.78 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 160.3 (*C*=C-*n*Bu), 140.4 (C-Tf), 135.5 ($C^{Ar\text{-}q}$), 132.0 ($C^{Ar\text{-}q}$), 130.0 (C=*C*-*n*Bu), 129.9 ($2CH^{Ar}$), 128.6 (CH-*Triazole*), 121.2 ($2CH^{Ar}$), 119.7 (q, J_{CF} = 331.2 Hz, $2CF_3$), 119.4 (q, J_{CF} = 324.8 Hz, CF_3), 86.3 (CTf_2), 36.7 (CH_2-*Cyclobutene*), 29.7 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 13.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.48 (s, 6F, $2CF_3$), –70.28 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1382, 1107 (O=S=O), 1216 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{16}N_3O_6S_3F_9$ [*M*]$^+$: 649.0058; found: 649.0066.

4-Triflyl triazole 111w. From 20 mg (0.11 mmol) of azide **110v**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **111w** (37 mg, 98%) as a colorless solid; mp 102–104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 5.65 (s, 2H, CH_2), 7.10 (d, 2H, *J* = 8.0 Hz, $2CH^{Ar}$), 7.36 (d, 2H, *J* = 8.5 Hz, $2CH^{Ar}$), 8.22 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 141.9 ($C^{Ar\text{-}q}$), 139.6 (C-Tf), 130.5 (CH-*Triazole*), 130.3 ($2CH^{Ar}$), 128.6 ($C^{Ar\text{-}q}$), 120.1 ($2CH^{Ar}$), 119.3 (q, J_{CF} = 324.6 Hz, CF_3), 54.7 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –78.55 (s, 3F, CF_3); IR ($CHCl_3$): ν = 2114 (N_3), 1379, 1114 (O=S=O), 1216 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{10}H_7N_6O_2SF_3$ [*M*]$^+$: 332.0303; found: 332.0310.

Bis(4-triflyl triazole) 111x. From 20 mg (0.11 mmol) of azide **110v**, and after recrystallization (acetonitrile) gave compound **111x** (42 mg, 78%) as a colorless solid; mp 181–183 ºC; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 6.02 (s, 2H, CH_2), 7.79 (d, 2H, *J* = 8.6 Hz, $2CH^{Ar}$), 8.09 (d, 2H, *J* = 8.6 Hz, $2CH^{Ar}$), 9.33 (s, 1H, CH-*Triazole*), 9.74 (s, 1H, CH-*Triazole*); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 ºC): δ = 140.0 (C-Tf), 139.3 (C-Tf), 137.6 ($C^{Ar\text{-}q}$), 137.3 ($C^{Ar\text{-}q}$), 134.4 (CH-*Triazole*), 132.6 (CH-*Triazole*), 131.4 ($2CH^{Ar}$), 123.0 ($2CH^{Ar}$), 120.52 (q, J_{CF} = 323.9 Hz, CF_3), 120.49 (q, J_{CF} = 323.9 Hz, CF_3), 54.9 (CH_2); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –80.18 (s, 3F, CF_3), –80.38 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1379, 1108 (O=S=O), 1216 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_8N_6O_4S_2F_6$ [*M*]$^+$: 489.9953; found: 489.9955.

Bis(4,5-dihydro-1*H*-1,2,3-triazole) 112s. From 21 mg (0.17 mmol) of azide **110s**, and after recrystallization (acetonitrile) gave compound **112s** (72 mg, quantitative yield) as a colorless solid; mp 147–149 ºC; ^{1}H NMR (300 MHz, $(CD_3)_2CO$, 25 ºC): δ = 5.44 (s, 2H, CH_2), 7.79 (d, 2H, *J* = 7.3 Hz, $2CH^{Ar}$), 8.88 (d, 2H, *J* = 7.3 Hz, $2CH^{Ar}$); ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 ºC): δ = 159.3 ($C^{Ar\text{-}q}$), 145.6 ($2CH^{Ar}$), 121.7 (q, J_{CF} = 326.0 Hz, $2CF_3$), 118.4 ($2CH^{Ar}$), 69.1 (CTf_2), 61.3 (CH_2); ^{19}F NMR (282 MHz, $(CD_3)_2CO$, 25 ºC): δ = –81.03 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 2124 (N–N=N), 1339, 1116 (O=S=O), 1167 (C–F) cm^{-1}; HRMS (ES): calcd for $C_9H_6N_4O_4S_2F_6$ [*M*]$^+$: 411.9735; found: 411.9742.

XI.4. Notes and references

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45 The regiochemistry of products **111** was unambiguously determined by the NOE analysis of **111h**.

46 Dihydroxy-triazoles **111i** and **111j** were in conformational equilibrium and conformers were observed by NMR spectroscopy. Both conformers were equilibrated after several hours in solution and converted into just one isomer.

47 Especies **INT1** is better described as a resonance hybrid between both dipolar and uncharged species.

48 Although the isolation of 4,5-dihydro-1*H*-1,2,3-triazole **112s** from the reaction of **110s** outlined in Scheme XI.2 was fortuitous, the result argues in favor of the mechanism shown in Scheme XI.4, because an observable intermediate of type **112** was formed.

XII. DISCUSIÓN GENERAL

XII. DISCUSIÓN GENERAL

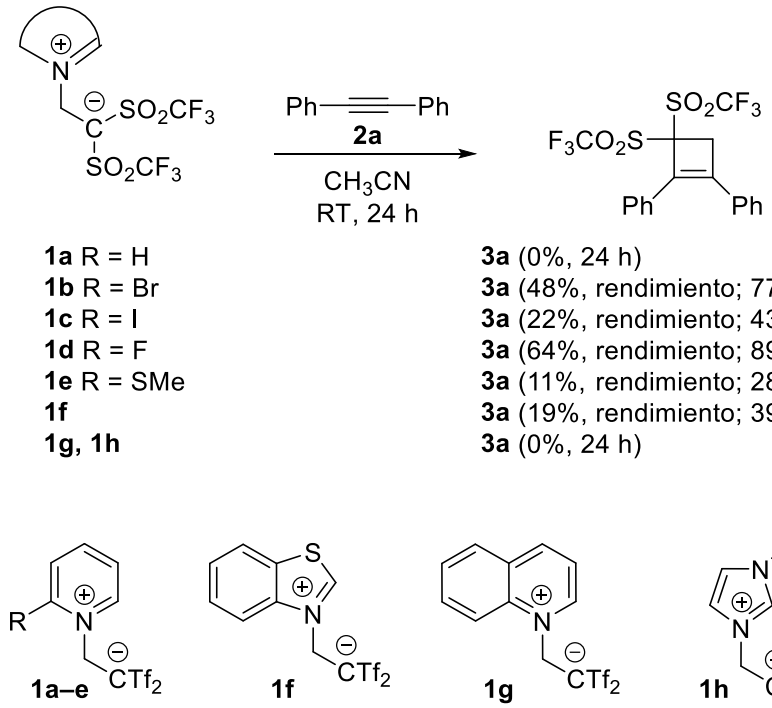
XII.1. Reacciones de zwitteriones de Koshar con alquinos.

A lo largo de esta sección se ha explorado la reactividad que presenta la molécula fuertemente polarizada $Tf_2C{=}CH_2$, generada *in situ* a partir de un zwitterión tipo Koshar, frente al grupo funcional alquino diferentemente sustituido.

XII.1.1. Capítulo 1: Descubriendo la reacción de alquinos con 1,2-dipolos para la síntesis no catalizada de ciclobutenos a temperatura ambiente

En este Capítulo se ha abordado el estudio de la reactividad de $Tf_2C{=}CH_2$ con alquinos simples terminales o internos (sustituidos por restos aromáticos y/o alifáticos).

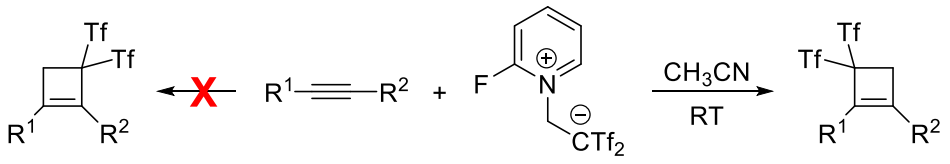
En primer lugar, se llevó a cabo la síntesis de diferentes zwitteriones de Koshar **1a-h**, variando los grupos sustituyentes en la piridina o bien cambiando directamente el heterociclo. Estos cambios van a modular el mayor o menor desplazamiento del equilibrio hacia la liberación de la molécula polarizada $Tf_2C{=}CH_2$ en disolución. Para determinar cuál de estas sales da mejores resultados, se hicieron reaccionar cada una de ellas con difenilacetileno **2a** a temperatura ambiente y utilizando acetonitrilo como disolvente (Esquema XII.1).



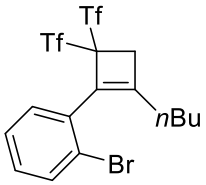
Esquema XII.1

Como resultado de estos ensayos se llegó a la conclusión de que la sal zwitteriónica de piridinio **1d** derivada de la 2-fluoropiridina es la más reactiva, pues permite obtener el ciclobuteno **3a** con un mayor rendimiento y conversión. También se exploró la posibilidad de cambiar tanto el disolvente como la temperatura inicialmente elegidos, pero el uso de acetonitrilo a temperatura ambiente resultó ser la combinación más adecuada para este proceso.

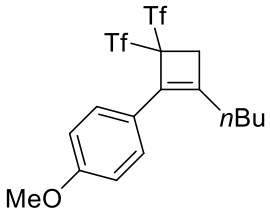
Con las condiciones de reacción optimizadas el siguiente paso fue estudiar la extensión de la metodología a otros alquinos simples no simétricos, diferentemente sustituidos por grupos alifáticos, aromáticos y heteroaromáticos (Esquema XII.2).



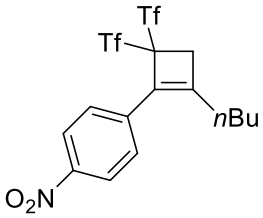
2b–o **1d** **3b–o**



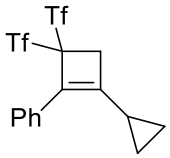
3b (59%, 5 h)



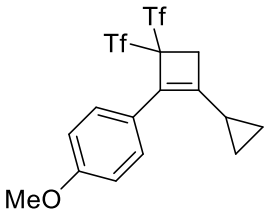
3c (96%, 5 h)



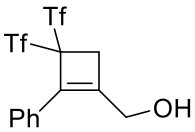
3d (25%, rendimiento basado en la conversión: 64%, 24 h)



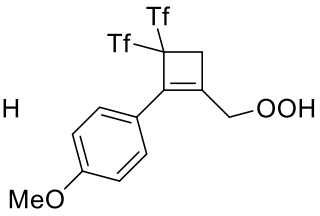
3e (41%, rendimiento basado en la conversión: 73%, 24 h)



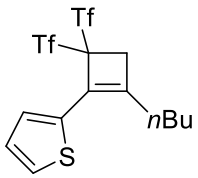
3f (51%, rendimiento basado en la conversión: 77%, 12 h)



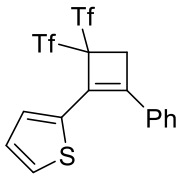
3g (72%, 12 h)



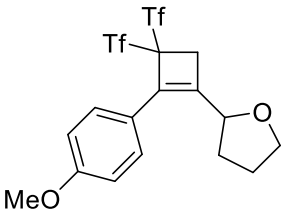
3h (68%, 5 h)



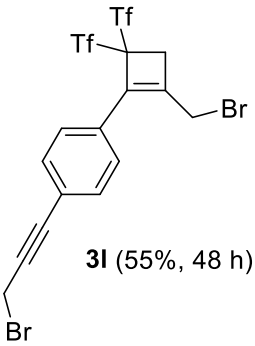
3i (74%, 4 h)



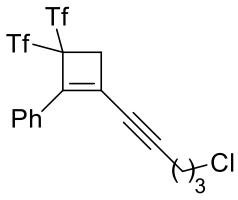
3j (56%, 24 h)



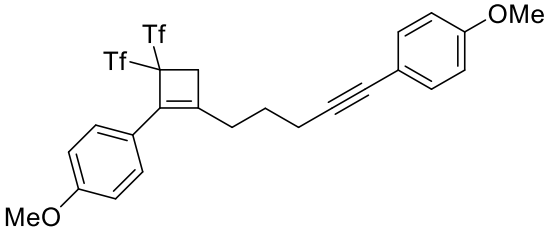
3k (75%, 5 h)



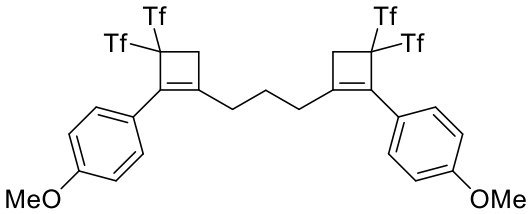
3l (55%, 48 h)



3m (53%, 48 h)



3n (47%, 4 h)



3o (86%, 4 h)

Esquema XII.2

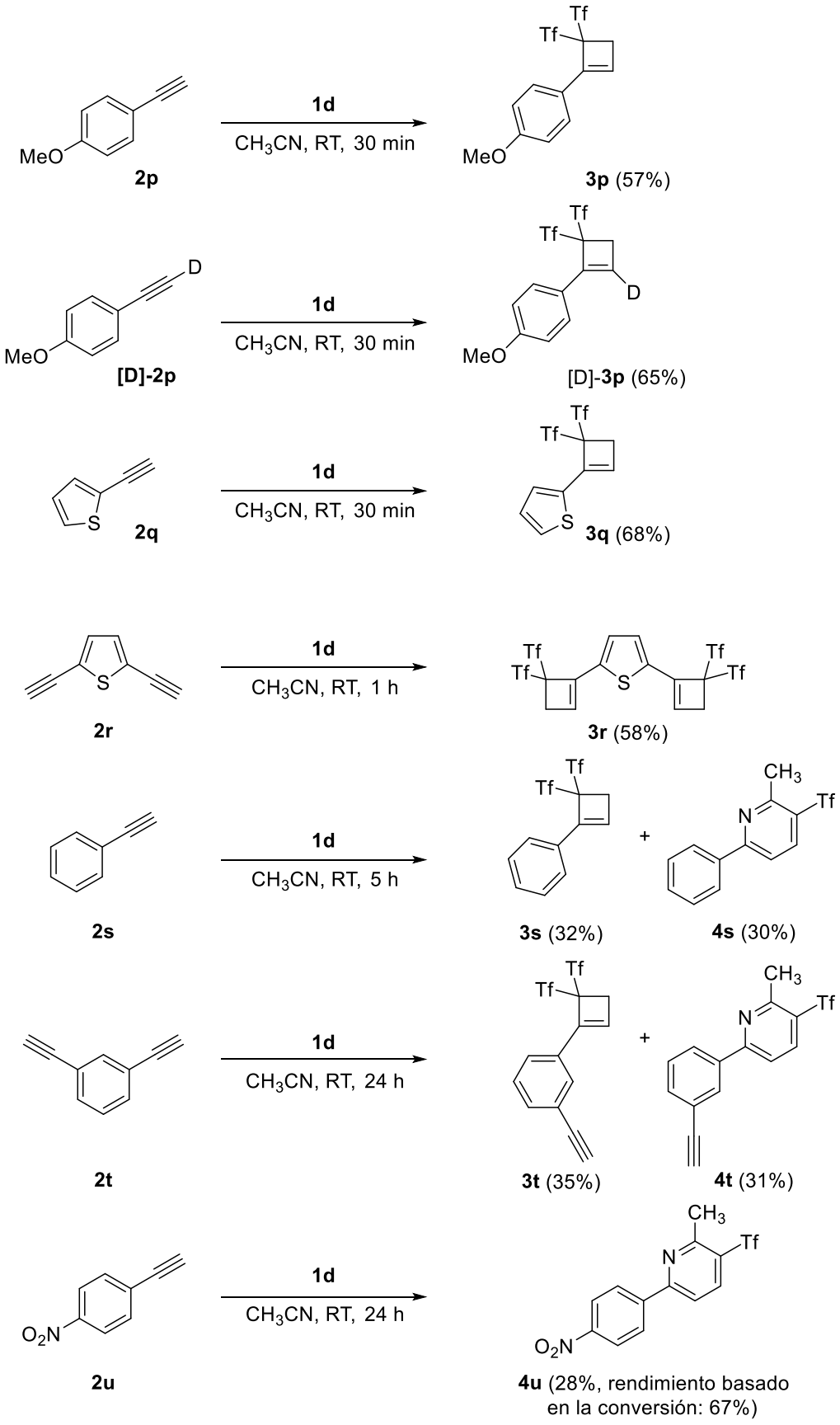
Los diferentes ejemplos obtenidos **3a−o** nos permitieron conocer algunas características importantes de esta reactividad. En primer lugar, el impedimento estérico no parece afectar significativamente al rendimiento de la reacción. Este hecho puede observarse con el alquino **2b**, donde un sustituyente relativamente voluminoso como es un átomo de bromo en posición *orto* no impide la formación del ciclobuteno **3b** con un rendimiento moderado. En segundo lugar, observamos que la naturaleza electrónica de los sustituyentes tiene una fuerte influencia en el curso de la reacción; así aquellos anillos aromáticos que poseen sustituyentes electro-dadores como **2c** permiten obtener el ciclobuteno correspondiente **3c** con un rendimiento muy alto si lo comparamos con su análogo **2d**, que presenta un grupo fuertemente electro-atractor como es el nitro y que conduce a la obtención de su ciclobuteno correspondiente **3d** con un pobre rendimiento. El mismo efecto podemos observar con los alquinos **2e** y **2f** aunque menos acusado que en el caso anterior. De igual manera heterociclos π-excedentes como el tiofeno en los ejemplos **2i** y **2j** conducen a los correspondientes ciclobutenos **3i** y **3j** satisfactoriamente. Sin embargo, cuando en estos sustratos sustituimos el tiofeno por un anillo π-deficiente (piridina) la reacción no funciona, recuperándose el material de partida.

Otra propiedad importante de la reacción directamente relacionada con las condiciones suaves empleadas, la observamos en los aductos **3g** y **3h**, que incorporan grupos funcionales sensibles como son un hidroxilo y sobre todo el hidroperóxido, que resultan inalterados en la reacción de formación de los ciclobutenos **3g** y **3h**. De igual manera, estas condiciones suaves permiten la reacción selectiva sobre uno o los dos triples enlaces del dialquino **2n**, jugando con los equivalentes de zwitterión **1d** utilizados y la velocidad de adición a la mezcla de reacción. Por último, una de las propiedades más importantes de todos estos procesos es sin duda su total regioselectividad. Cada alquino ensayado sería, en teoría, capaz de originar dos regiosómeros. Sin embargo, en ningún caso, ni siquiera a nivel de trazas, se observa la formación del regioisómero contrario.

Dada la utilidad sintética que pueden tener los ciclobutenos, resulta interesante su escalado para obtener cantidades en el orden de gramos. Afortunadamente, al aumentar la cantidad de material de partida a la escala de 5 mmol con el alquino **2g**, se obtuvo el correspondiente ciclobuteno **3g** con un 77% de rendimiento.

Una vez estudiados los alquinos disustituidos, nos centramos en los alquinos terminales. Los primeros ensayos realizados sobre alquinos terminales alifáticos no originaron ningún producto, recuperándose el material de partida inalterado. De nuevo, queda patente la importancia de la naturaleza electrónica de los sustituyentes.

Dado que los alquinos terminales con un sustituyente alifático dieron resultados negativos decidimos centrarnos en aquellos sustituidos por anillos aromáticos. Estos, al contrario que los primeros, presentan una alta reactividad, los resultados obtenidos están recogidos en el Esquema XII.3.



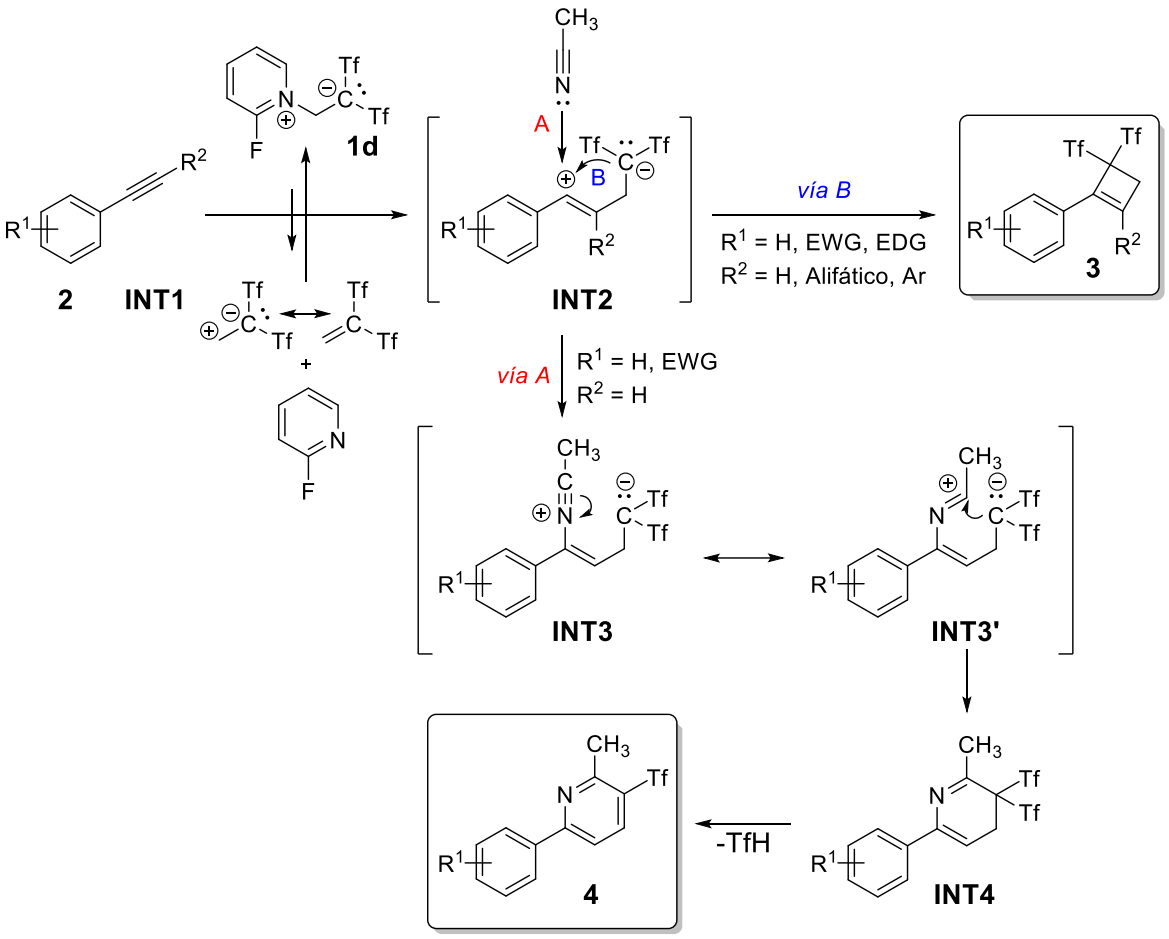
Esquema XII.3

Los primeros ejemplos, donde el alquino está sustituido por un arilo activado **2p** y [D]-**2p**, conducen a la formación de los ciclobutenos esperados. De igual manera ocurre cuando en el alquino se encuentra un anillo π-excedente (tiofeno) como ocurre en el caso **2q**. También es posible la formación simultanea de dos ciclobutenos a partir del dialquino terminal **2r** en las mismas condiciones.

La primera diferencia en cuanto a reactividad, respecto a los alquinos disustituidos, la encontramos al hacer reaccionar el fenilacetileno **2s** con el zwitterión **1d** en las mismas condiciones empleadas anteriormente. En este caso, se obtiene una mezcla del ciclobuteno esperado **3s** y de la piridina **4s**. La formación de esta piridina solo puede explicarse si consideramos la participación de una molécula de acetonitrilo en la reacción. Un comportamiento similar encontramos con el 1,3-dietinilbenceno **2t** que origina la mezcla de ciclobuteno **3t** y piridina **4t** en proporción 1:1. En ambos casos uno de los alquinos terminales iniciales queda inalterado. Aunque la quimioselectividad en estos casos es nula hay que destacar que ambos productos son fáciles de separar por cromatografía en columna sobre gel de sílice, lo que proporciona el acceso a dos productos cíclicos valiosos. Por último, queríamos conocer el comportamiento de un alquino terminal con un sustituyente desactivante. Se eligió el alquino **2u** como sustrato modelo con un grupo nitro en la posición *para* del anillo bencénico. Aplicando las condiciones de reacción anteriores, se obtiene únicamente la piridina **4u** con bajo rendimiento.

Por tanto, queda patente la importancia crítica que tiene la naturaleza electrónica de los sustituyentes para modular la reactividad.

Apoyándonos en cálculos DFT realizamos una propuesta mecanística para explicar la formación de los ciclobutenos **3** y las piridinas **4** (Esquema XII.3 y Figura XII.1).



Esquema XII.3

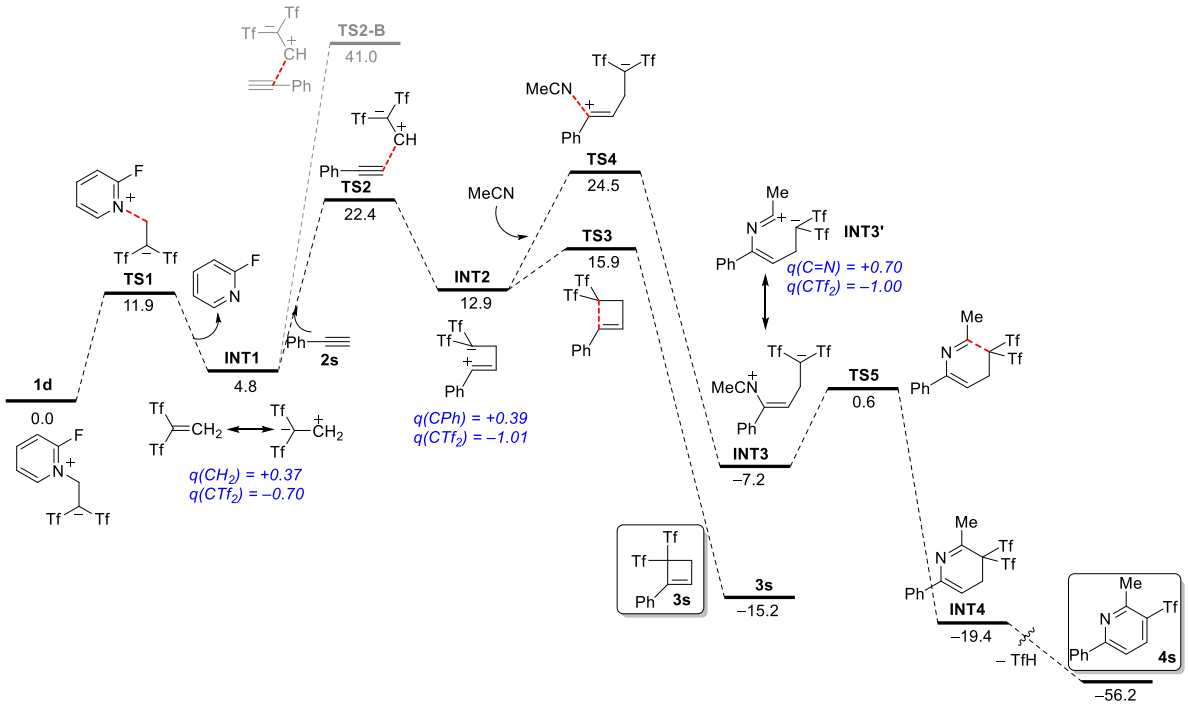


Figura XII.1

En primer lugar, el zwitterión **1d** en disolución entra en un equilibrio en el que se libera el 1,1-bis(trifluorometillsulfonil)eteno **INT1**, alqueno altamente polarizado cuya forma resonante como 1,2-dipolo va a ser la responsable de reaccionar con el triple enlace. En este proceso se libera 2-fluoropiridina, la cual es fácil de eliminar experimentalmente al ser un producto volátil. El siguiente paso implica la formación de un nuevo enlace C−C entre el carbono terminal del alquino y el 1,2-dipolo, lo que origina la formación del carbocatión vinílico intermedio **INT2** común a ambos procesos. La estabilización de este carbocatión vinílico **INT2** a través del anillo aromático explica el hecho empírico de que la reacción este favorecida por grupos electro-dadores. Además, también se explica la total regioselectividad del proceso, pues la obtención hipotética del intermedio catiónico correspondiente al otro regioisómero posible implicaría una alta energía de activación a través del estado de transición **TS2-B**, dado que no puede estabilizarse por deslocalización en el arilo.

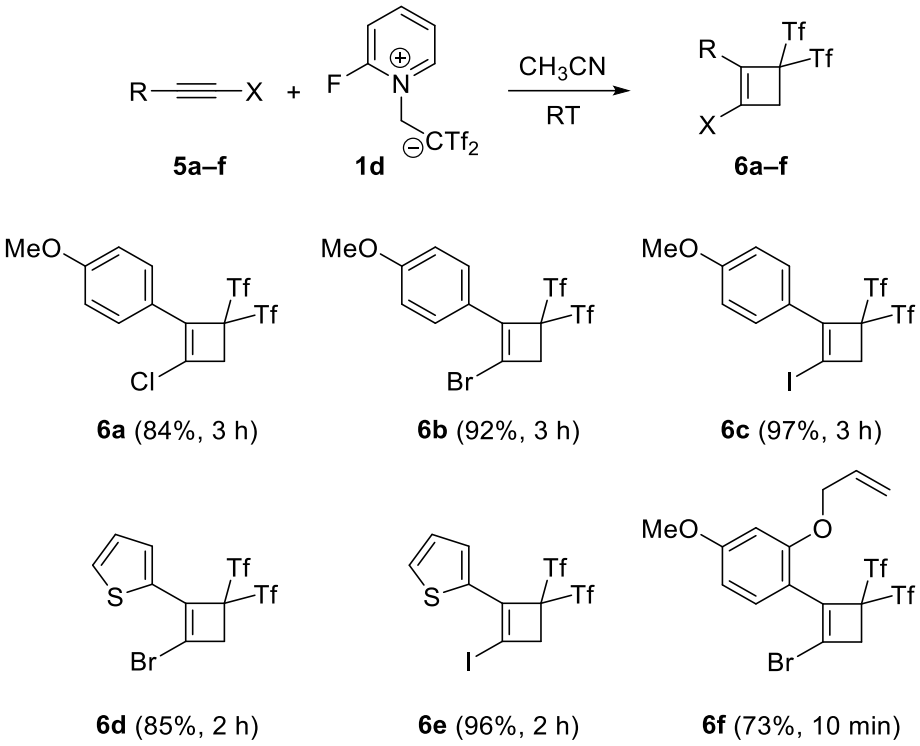
El carbocatión vinílico **INT3** puede cerrarse para originar el ciclobuteno **3** (*vía* B) o bien puede producirse la adición nucleófila del disolvente acetonitrilo (*vía* A). Esto implica la formación de una nueva especie zwitteriónica **INT3** cuya forma resonante **INT3'** sufre el cierre del anillo para generar el heterociclo **INT4**. Finalmente, se produce la eliminación de uno de los grupos Tf, expulsado en forma de TfH, que conduce a la formación de la piridina **4**. Sin duda, la fuerza impulsora de este último proceso es la aromatización del anillo en una etapa irreversible, lo cual es un factor de estabilización excepcional.

XII.1.2. Capítulo 2: Síntesis regioselectiva de bis-(trifil)ciclobutenos funcionalizados con heteroátomos

Una vez explorada la reactividad de los zwitteriones de Koshar con alquinos sencillos, decidimos extender la metodología a alquinos que presentan un heteroátomo del bloque *p* unido directamente a uno de los C(sp^3) del triple enlace. Estos heteroátomos van a modificar las propiedades del alquino, variando en algunos casos su reactividad.

Iniciamos nuestro estudio con alquinos que contienen un átomo de halógeno. Como sustrato modelo elegimos el 1-cloroalquino **5a**. Partimos de las mismas condiciones optimizadas del trabajo anterior, acetonitrilo como disolvente y temperatura ambiente, obteniéndose el clorociclobuteno **6a** con buen rendimiento, como un solo regioisómero y sin la necesidad de catalizador. Aun así, se probaron diversas combinaciones de disolvente y temperatura, pero ninguna consiguió superar los rendimientos alcanzados con las condiciones iniciales. Hay que destacar que el zwitterión **1d** es poco soluble en disolventes apolares o halogenados a temperatura ambiente, lo que limita bastante la elección de disolvente.

Establecidas las condiciones optimizadas, se aplicaron a los diferentes 1-bromo(yodo)alquinos **5b-f**, los cuales contienen bromo o yodo como sustitución halogenada y anillos aromáticos o heteroaromáticos, obteniéndose los cicloaductos **6b-f** (Esquema XII.4).



Esquema XII.4

Estas variaciones estructurales nos permitieron conocer la influencia de los sustituyentes halogenados en la reactividad. El cambio del átomo de halógeno no afecta significativamente a la reactividad; sin embargo, el uso de anillos más electrodadores sí que acelera la reacción, como podemos observar en el ejemplo **6f**, en el cual la reacción se completa en tan solo 10 minutos. Para tener certeza de la regioquímica se llevó a cabo el análisis por rayos X de monocristal del aducto **6d** (Figura XII.2).

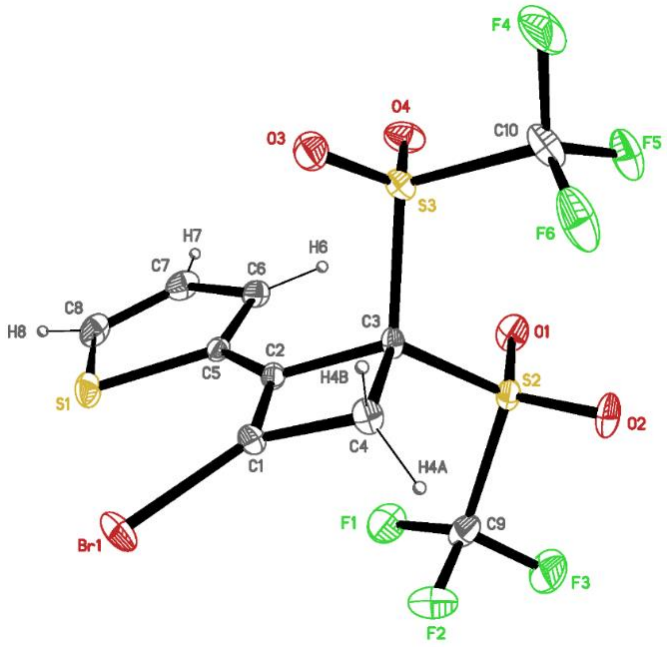
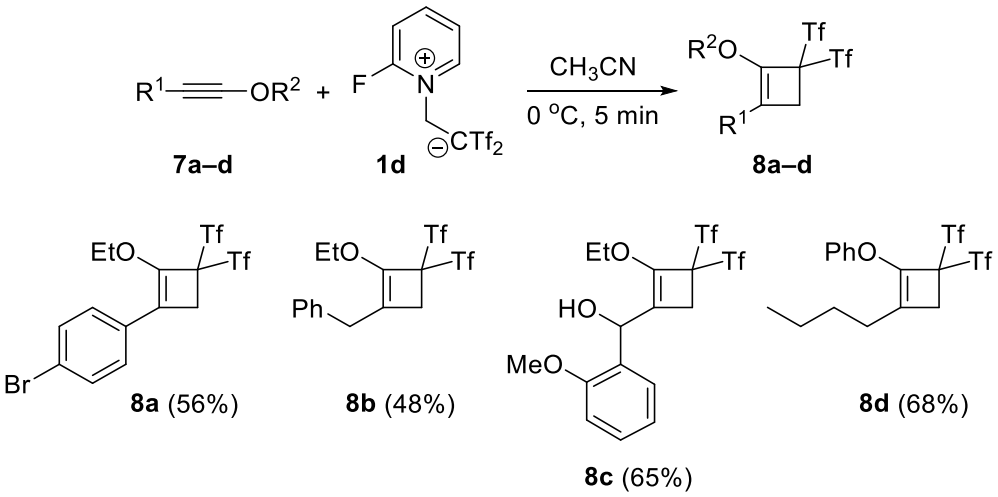


Figura XII.2

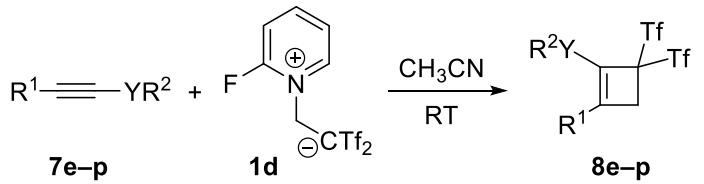
Una vez preparados los halociclobutenos, continuamos nuestro trabajo centrándonos en el grupo de los alquiniléteres **7a-d**. Cuando aplicamos las mismas condiciones de reacción que en el caso de los haloalquinos, observamos unos rendimientos bajos. Esto se debe a que los inoléteres son muy reactivos y generan subproductos. Una modificación simple de las condiciones, bajando la temperatura de reacción a 0ºC, fue suficiente para obtener los enoléteres cíclicos **8a-d** con rendimientos razonables y en tiempos de reacción extremadamente cortos (Esquema XII.5).



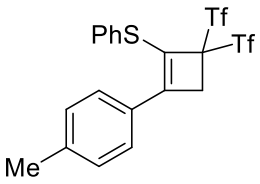
Esquema XII.5

Una característica muy importante que observamos con este tipo de alquino es que la presencia del grupo OR en los materiales de partida modifica radicalmente la regioquímica de la reacción. Hasta ahora, el anillo aromático presente en el alquino de partida dictaba qué regioisómero se obtenía. En este caso es el heteroátomo oxígeno el que dirige la regioselectividad. Esto permite que puedan sintetizarse por este método ciclobutenos **8b-d**, donde la dependencia de la presencia de un anillo aromático directamente unido al triple enlace se ha eliminado. Además, la reacción es tan regioselectiva que aun en presencia de un anillo aromático, como ocurre en el alquino de partida **7a**, se obtiene el ciclobutenileter **8a** como único regioisómero, sin detectarse la formación del otro posible.

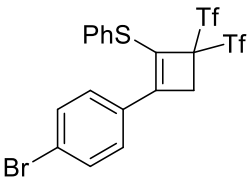
Animados por este resultado, decidimos seguir explorando la reactividad en alquinos que incorporan otros átomos del grupo de los anfígenos, es decir, con azufre, selenio y teluro. Para ello se prepararon una serie de alquinos **7e-p** que contienen estos heteroátomos como sustituyentes en el triple enlace. Aplicando las condiciones optimizadas iniciales a los tio-alquinos **7e-j**, se obtuvieron los tio-ciclobutenos **8e-j** con buenos rendimientos. En este caso no es necesario enfriar la reacción pues los tio-alquinos son menos reactivos que los inoléteres, lo cual se refleja en la diferencia de tiempos de reacción. Sin embargo, se obtiene el mismo nivel y tipo de regioselectividad que en los derivados de oxígeno (Esquema XII.6).



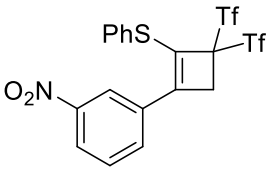
7e–p **1d** **8e–p**



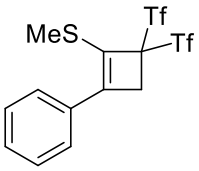
8e (70%, 10 min)



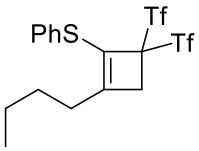
8f (93%, 4 h)



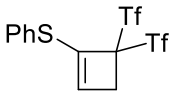
8g (86%, 30 min)



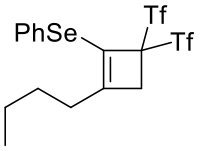
8h (90%, 10 min)



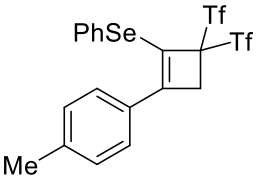
8i (70%, 5 min)



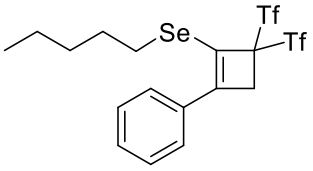
8j (71%, 5 min)[a]



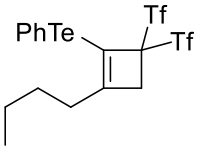
8k (75%, 5 min)



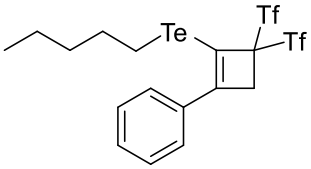
8l (43%, 10 min)[b]



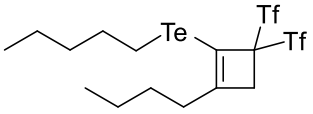
8m (rendimiento cuantitativo, 5 min)



8n (73%, 5 min)



8o (80%, 10 min)



8p (rendimiento cuantitativo, 5 min)

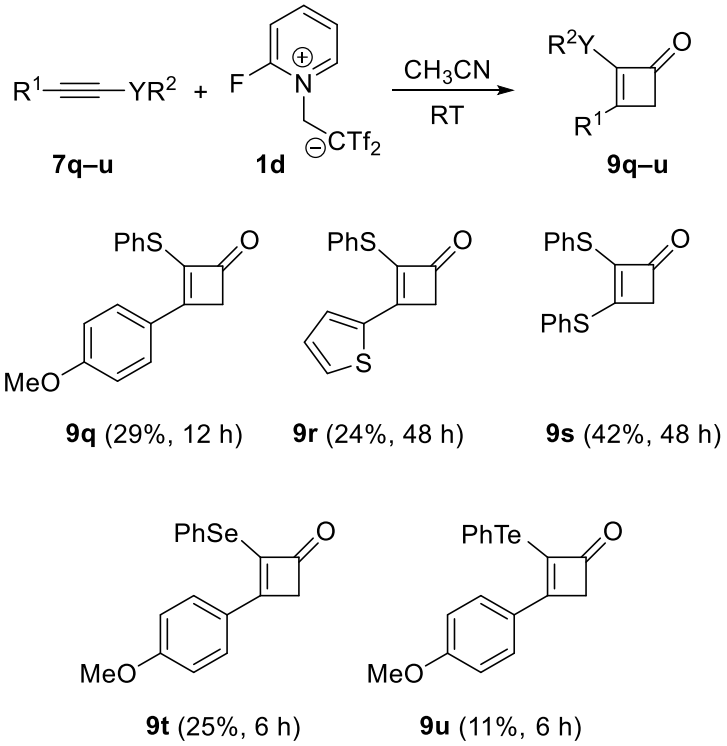
[a] La reacción se llevó a cabo a 0ºC.

[b] Descomposición parcial durante la purificación por cromatografía en columna.

Esquema XII.6.

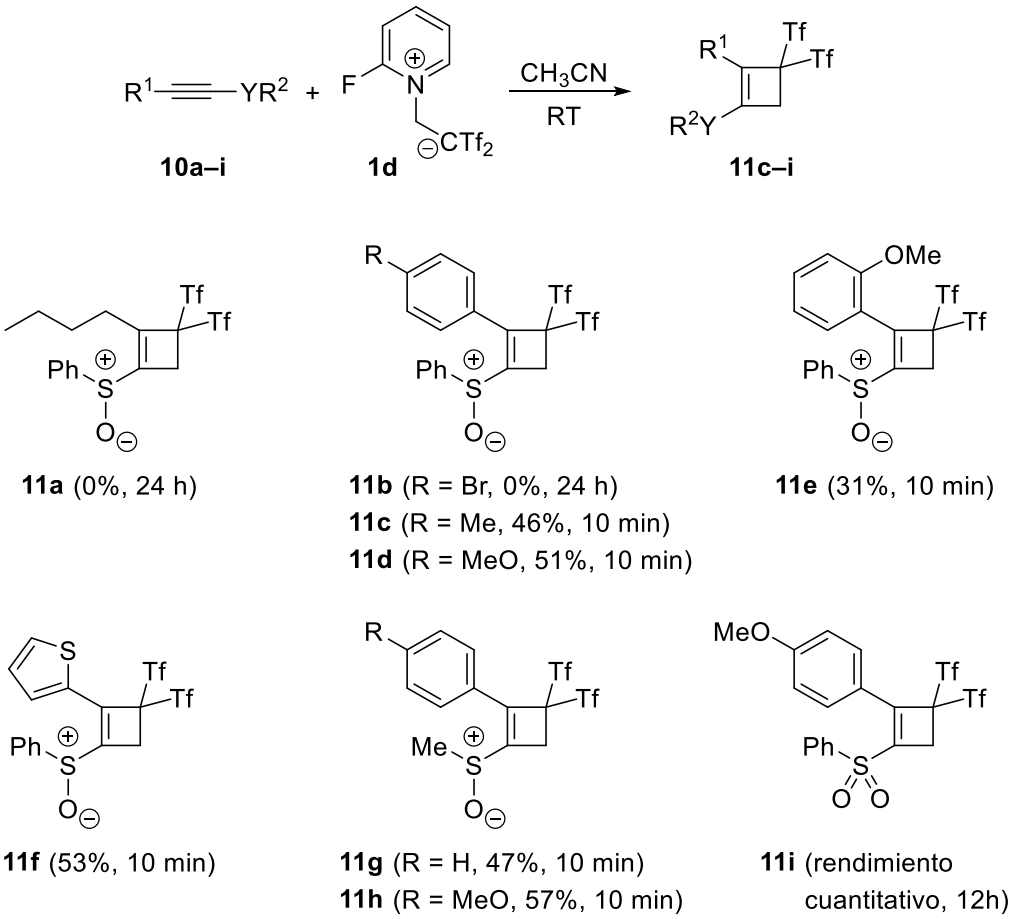
La ciclación de los precursores **7k-p** que contienen selenio y teluro en su estructura condujo a la formación de los ciclobutenos **8k-p** (Esquema XII.6). Los rendimientos de estos productos fueron muy buenos y su estabilidad alta, a excepción del derivado de selenio **8l**, que sufre descomposición parcial durante su purificación por cromatografía en columna sobre gel de sílice. En todos los casos se observa el mismo regiocontrol que con los derivados de oxígeno y azufre.

Aquellos sustratos **7q-u** que contienen un calcógeno y un sustituyente rico en electrones en la otra posición del triple enlace presentan una reactividad particular. Cuando se aplican las condiciones estándar utilizadas hasta ahora a estos sustratos, se obtienen las ciclobutenonas inesperadas **9q-u**. Estas pueden aislarse fácilmente, pero por análisis en CCF se observa que su formación viene acompañada con una serie de subproductos que forman una mezcla compleja, causa por la cual su rendimiento es bajo (Esquema XII.7).



Esquema XII.7

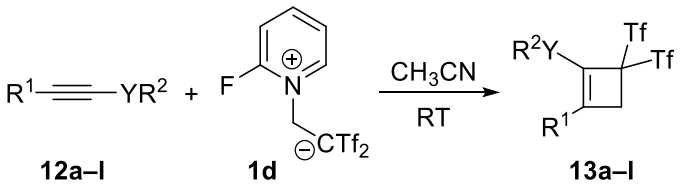
El estado de oxidación del azufre en los alquinos precursores se puede modificar por oxidación parcial (sulfóxidos) o total (sulfonas) y conocer cómo afecta a la reacción frente al zwitterión **1d**. De esta manera se estudió la reactividad de los sulfinilalquinos **10a-h** y del sulfonilalquino **10i** (Esquema XII.8).



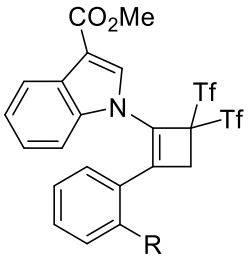
Esquema XII.8

Inicialmente se estudiaron los sulfinilalquinos electro-deficientes con sustituyente alifático **10a** o con anillo desactivante **10b**, que permanecieron inertes en la reacción, recuperándose el material de partida. Por el contrario, los sulfinilalquinos con anillos aromáticos neutros (fenilo) **10g** o ricos en electrones **10c-f** y **10h** permitieron el acceso a los sulfinilciclobutenos **11c-h** con rendimientos moderados. El mismo comportamiento lo encontramos en la alquinilsulfona **10i**, que condujo al sulfociclobuteno **11i**, pero con excelente rendimiento. El aspecto más importante observado en estos resultados es la regioquímica inversa que se obtiene cuando pasamos de átomo de azufre en estado de oxidación -2 (alquinos **7e-j**) a estado de oxidación +4 (alquinos **10c-h**) y +6 (alquino **10i**). La oxidación del azufre provoca que el heteroátomo pierda la capacidad de dirigir la regioquímica, que vuelve a estar gobernada por los anillos aromáticos como en el caso de los halo-ciclobutenos **6a-f**.

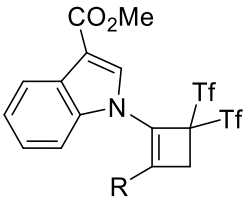
En este punto nos planteamos explorar la reactividad de triples enlaces con la introducción de un átomo de nitrógeno. Para ello incorporamos el nitrógeno a través de un anillo de indol. Este tipo de alquino se denomina inamina. Las inaminas **12a-l** condujeron satisfactoriamente a la preparación de los ciclobutenos **13a-l** como únicos productos con buenos rendimientos en general (Esquema XII.9).



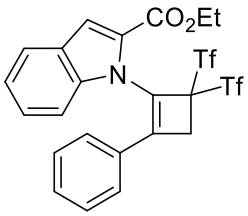
12a–l **1d** **13a–l**



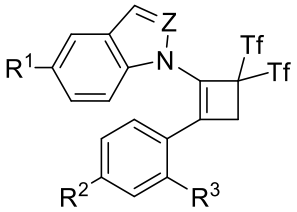
13a R = H (94%, 4 h)
13b R = MeO (33%, 3 h)



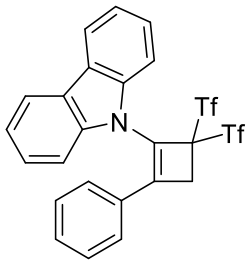
13c R = H (67%, 1 min)[a]
13d R = 2-tienil (29%, 1 h)
13e R = 3-$MeOC_6H_4$ (95%, 2 h)
13f R = 3-$NO_2C_6H_4$ (82%, 5 h)
13g R = *n*-Bu (84%, 5 min)



13h (rendimiento cuantitativo, 1 h)



13i R^1 = H, R^2 = H, R^3 = H, Z = N (rendimiento cuantitativo, 3 h)
13j R^1 = H, R^2 = H, R^3 = MeO, Z = N (40%, 1 h)
13k R^1 = Br, R^2 = Br, R^3 = H, Z = CH (72%, 30 min)



13l (88%, 1 min)

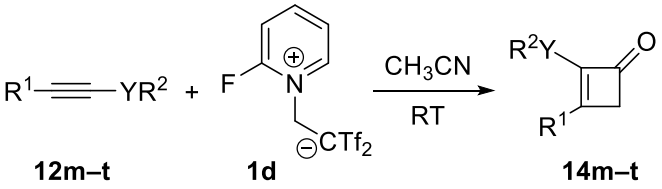
[a] La reacción se llevó a cabo a 0ºC.

Esquema XII.9

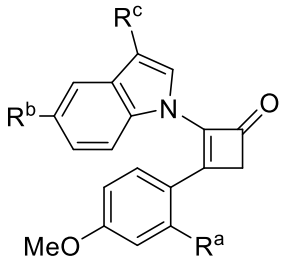
De nuevo, en lo referente a la regioquímica, el nitrógeno toma fuertemente el control y dirige la formación de un único regioisómero como ocurría con otros heteroátomos con pares de electrones libres (O, S, Se, Te).

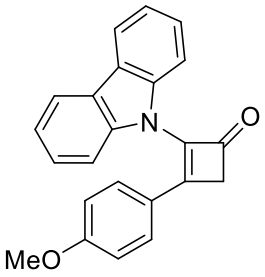
Un resultado inesperado lo encontramos en las inaminas **12m-t** que poseen un anillo rico en electrones (4-$MeOC_6H_4$) y que al aplicar las condiciones generales

de reacción conducen a las ciclobutenonas **14m-t** (Esquema XII.10), de manera semejante a lo que ocurría con alquinos ricos en electrones **7q-u**.

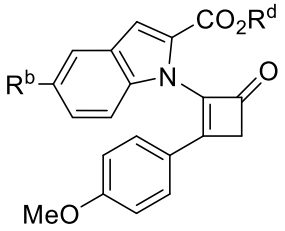


12m–t **1d** **14m–t**





14p (88%, 12 h)



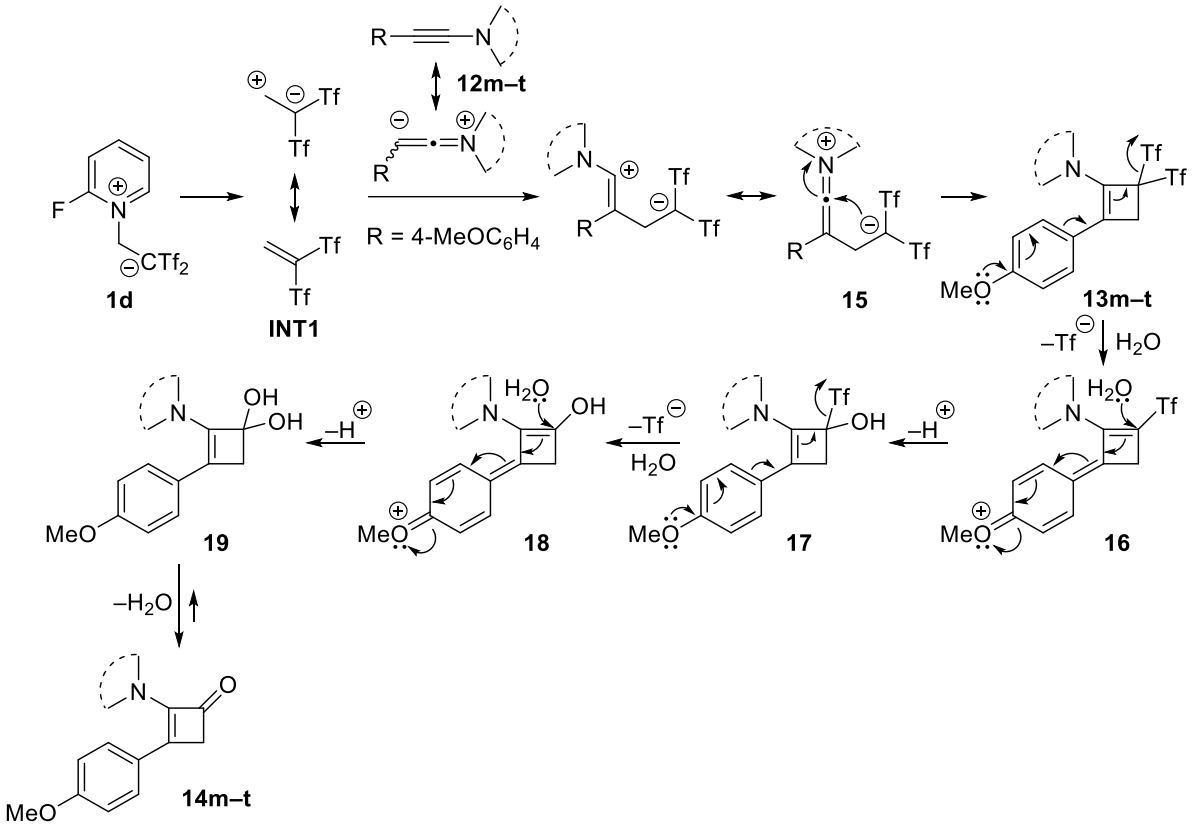
14m R^a = H, R^b = H, R^c = CO_2Me (86%, 12 h)
14n R^a = MeO, R^b = H, R^c = CO_2Me (23%, 12 h)[a]
14o R^a = H, R^b = Br, R^c = H (42%, 12 h)

14q R^b = H, R^d = Et (53%, 12 h)
14r R^b = Me, R^d = Et (45%, 12 h)
14s R^b = Cl, R^d = Et (51%, 12 h)
14t R^b = H, R^d = Ph (41%, 72 h)

[a] Mezcla de compleja de reacción.

Esquema XII.10

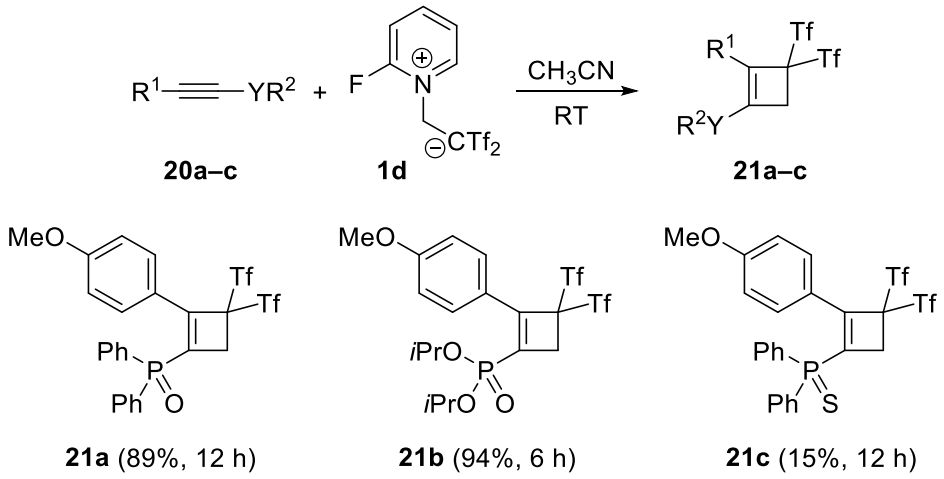
El mecanismo propuesto para explicar la formación de ciclobutenonas involucra a dos procesos principales, por un lado, la construcción inicial del anillo de ciclobuteno y por otro la formación de un grupo carbonilo (Esquema XII.11).



Esquema XII.11

La propuesta para el primer proceso está basada en el estudio DFT realizado en el trabajo anterior (Capítulo 1) pero en este caso, como se ha comentado anteriormente, la regioselectividad está regida por los efectos electrónicos del heteroátomo. La presencia de agua en el disolvente empleado y la humedad ambiental es suficiente para que se produzca la doble eliminación de trifluoro(hidrosulfonil)metano (TfH) que origina los bis(hidroxi)ciclobutenos **19**. Esta entrada de dos moléculas de agua en la estructura está asistida por el efecto de resonancia que producen los sustituyentes aromáticos activados, especialmente el grupo metoxilo en el anillo de 4-metoxifenilo. Finalmente, se produce una deshidratación del aducto **19** que origina las ciclobutenonas **14m-t**. De manera semejante se obtienen las ciclobutenonas equivalentes **9q-u**.

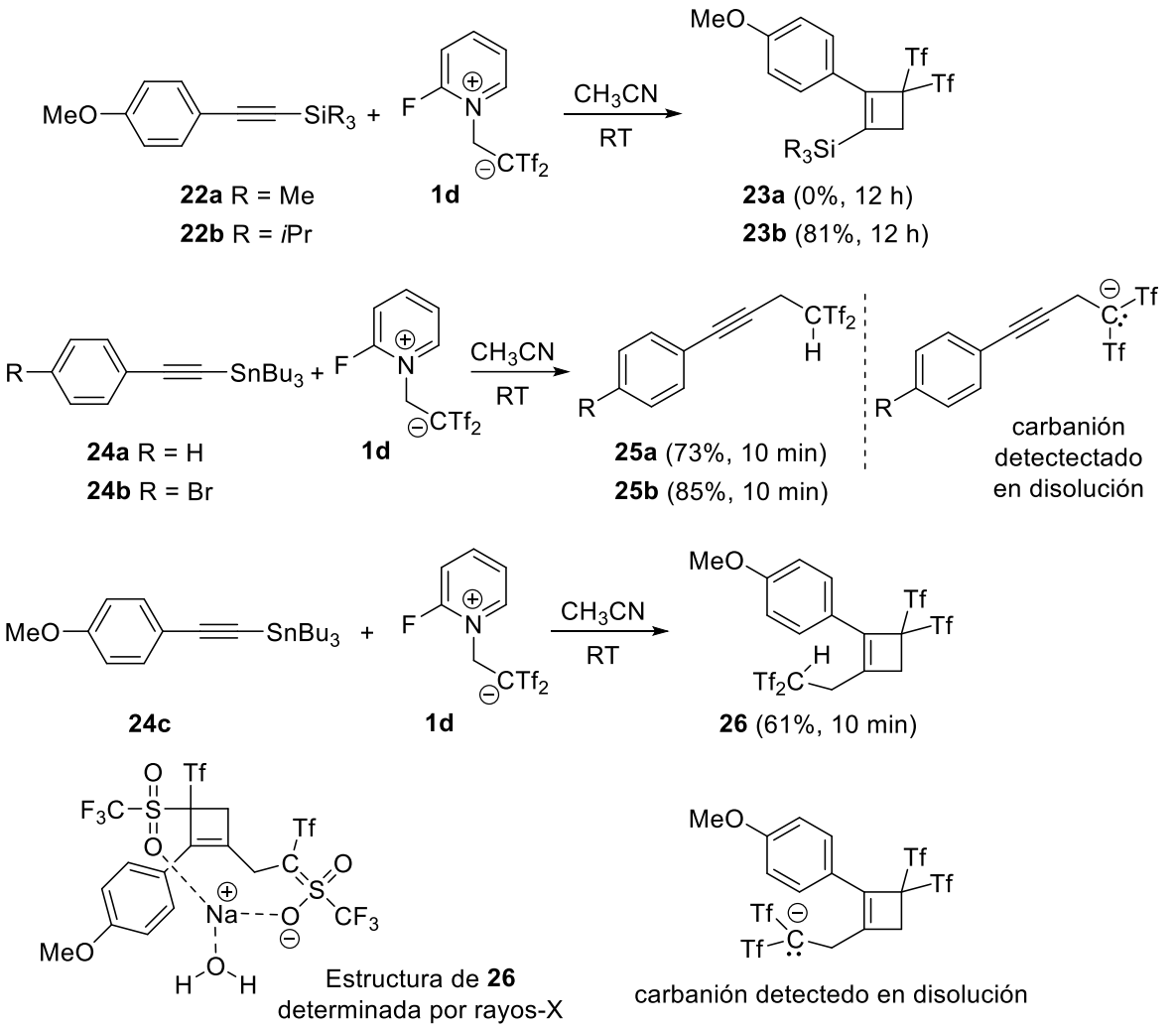
El siguiente heteroátomo enlazado a un triple enlace que decidimos examinar fue el fósforo. Concretamente se estudió la reacción sobre los sustratos **20** en los que el fósforo se encuentra en forma de óxido de fósforo **20a**, fosfonato **20b** y sulfuro de fósforo **20c** (Esquema XII.12).



Esquema XII.12

Para los tres casos el átomo de fósforo se encuentra desprovisto de pares de electrones libres, lo que condiciona la reactividad del propio alquino. De este modo, al aplicar las condiciones generales de reacción se obtienen los fosforilciclobutenos **21a** y **21b** con excelente rendimiento mientras que **21c** se aísla con un rendimiento muy pobre. Aun así, para los tres ejemplos, la regioselectividad vuelve a ser total, donde el grupo arilo dicta qué regioisómero se forma. El estudio de la reactividad sobre alquinilfosfinas, donde el fósforo dispone de un par de electrones libre (de manera análoga a un grupo amino) será tratada en el Capítulo 6 de manera independiente.

Teniendo en cuenta el peso que tienen en Química Orgánica los organosilanos y los estannanos, pensamos que era importante conocer la influencia de estos dos elementos en la reactividad de los alquinos. Cuando llevamos a cabo la reacción sobre el sustrato sililado **22a** la formación del correspondiente TMS-ciclobuteno **23a** se detectó por CCF, pero no fue posible su aislamiento posterior debido posiblemente a la labilidad propia de este silano (Esquema XII.13).



Esquema XII.13

Por ello, preparamos el alquino **22b**, donde el triisopropilsilano debería ofrecer una mayor resistencia a la ruptura del enlace C−Si, pero a costa de aumentar considerablemente el impedimento estérico. Afortunadamente, como se ha visto anteriormente, los efectos estéricos no influyen demasiado en las cicloadiciones [2+2] de la molécula $Tf_2C{=}CH_2$, lo que nos permitió la síntesis del sililciclobuteno **23b** eliminándose los problemas de labilidad del grupo trimetilsilano en su aislamiento.

Al llevar a cabo la reacción sobre el alquinilestannano **24a** se obtuvo el producto inesperado **25a** donde el triple enlace queda inalterado y el grupo Bu_3Sn es sustituido por el resto alifático CH_2CHTf_2 derivado de la molécula $H_2C{=}CTf_2$. Un resultado equivalente se obtiene con el sustrato **24b** que conduce al alquino alquilado **25b**. Con la intención de aumentar la reactividad del triple enlace se preparó el sustrato **24c**, portador de un arilo activado. Este alquinilestannano permite

acceder al tetrakis(trifluorometanosulfonil)ciclobuteno **26c** con un 61% de rendimiento en tan solo 10 min. Las moléculas **25a**, **25b** y **25c** portadoras del resto CH_2CHTf_2, disocian fácilmente el hidrógeno ácido dando carbaniones estables en disolución. Además, por esta misma razón, las señales de este protón ácido en ^{1}H-RMN no se detectan. Es importante señalar que al hacer pasar estos productos por gel de sílice durante su purificación el protón ácido se intercambia por un catión sodio, por lo que se aíslan como sales orgánicas de sodio como se manifiesta en el análisis por rayos X de monocristal del producto **26c** (Figura XII.3).

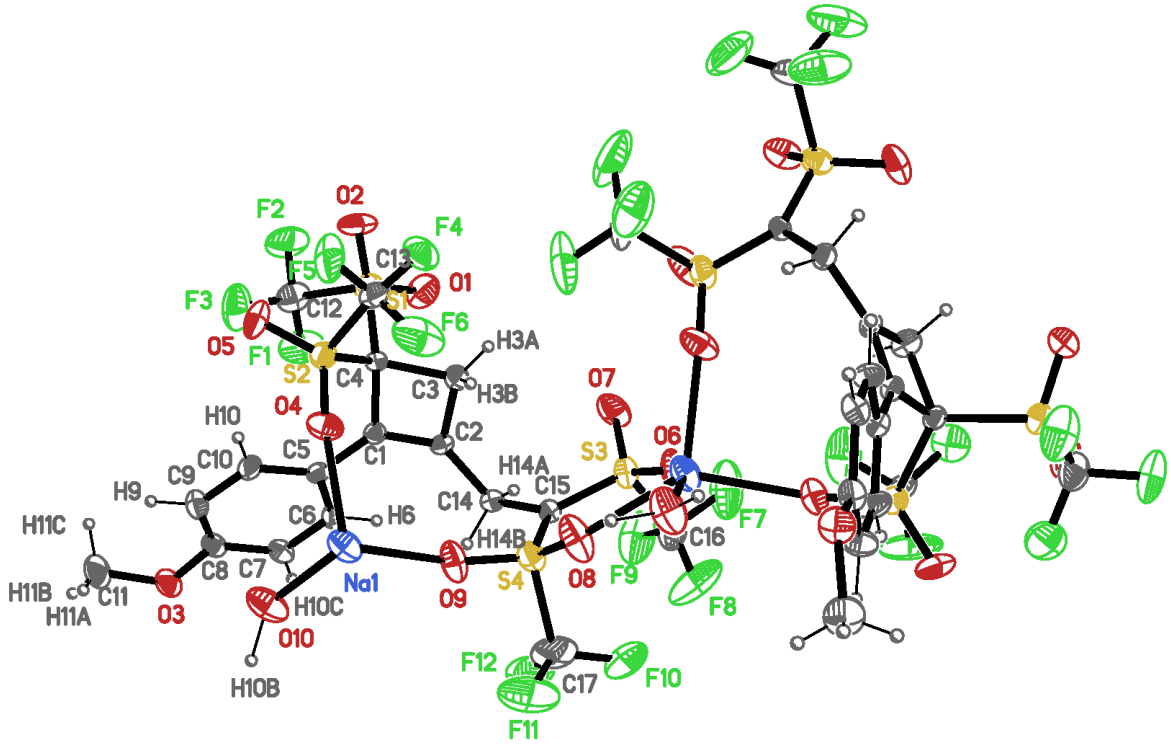
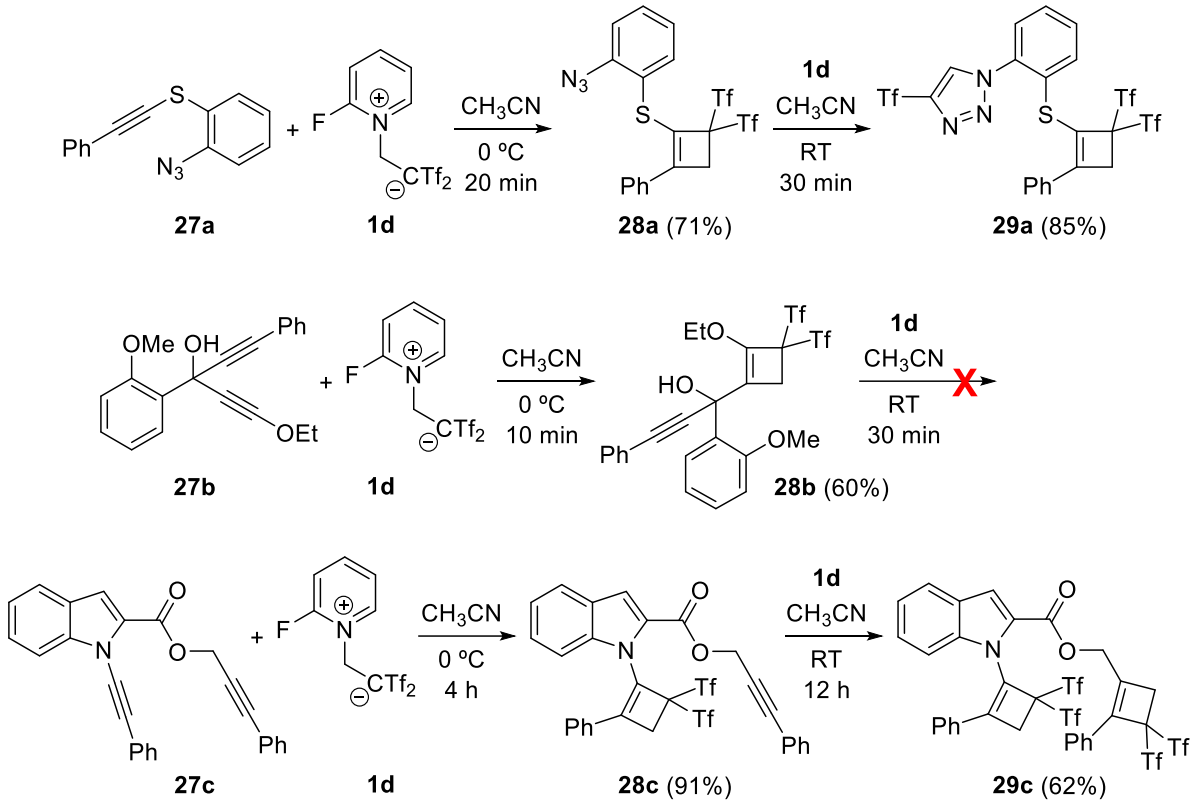


Figura XII.3

Una vez completado el estudio sobre los diferentes alquinos y la influencia de los heteroátomos en su reactividad, pensamos que sería interesante funcionalizar selectivamente diferentes grupos funcionales dentro de una misma molécula. Los sustratos preparados **27a-c** se hicieron reaccionar en las mismas condiciones generales de reacción ya descritas (Esquema XII.14).



Esquema XII.14

Cada reacción permite obtener con total selectividad los ciclobutenos **28a-c**, en las cuales la monociclación del alquino sustituido con un heteroátomo está favorecida. La bis-funcionalización del alquino o azida remanente se lleva a cabo al añadir un segundo equivalente de zwitterión **1d**, ya que al tratarse de grupos funcionales menos reactivos dan lugar a una exquisita selectividad.

La reacción de formación de triazoles a partir de azidas, como es el caso de **29a**, se tratará en detalle en el Capítulo 8 de la presente Memoria.

XII.1.3. Capítulo 3: Acceso directo y sin uso de metales a aminociclobutenos o aminociclobutenoles desde inamidas: Aplicaciones sintéticas

Tras haber estudiado la reactividad de las inaminas en el Capítulo anterior, observamos que otro grupo importante de alquinos nitrogenados presentaba una química particular al enfrentarlos a la molécula altamente polarizada $Tf_2C{=}CH_2$. Se trata del grupo de las inamidas. En este caso, el nitrógeno unido al triple enlace está enlazado a su vez a un grupo carbonilo, lo que va a modificar su reactividad en algunos casos. Este hecho nos llevó a realizar un estudio en profundidad que ha desembocado en el presente Capítulo.

Inicialmente se prepararon una serie de inamidas de partida, con una amplia diversidad estructural (Figura XII.4).

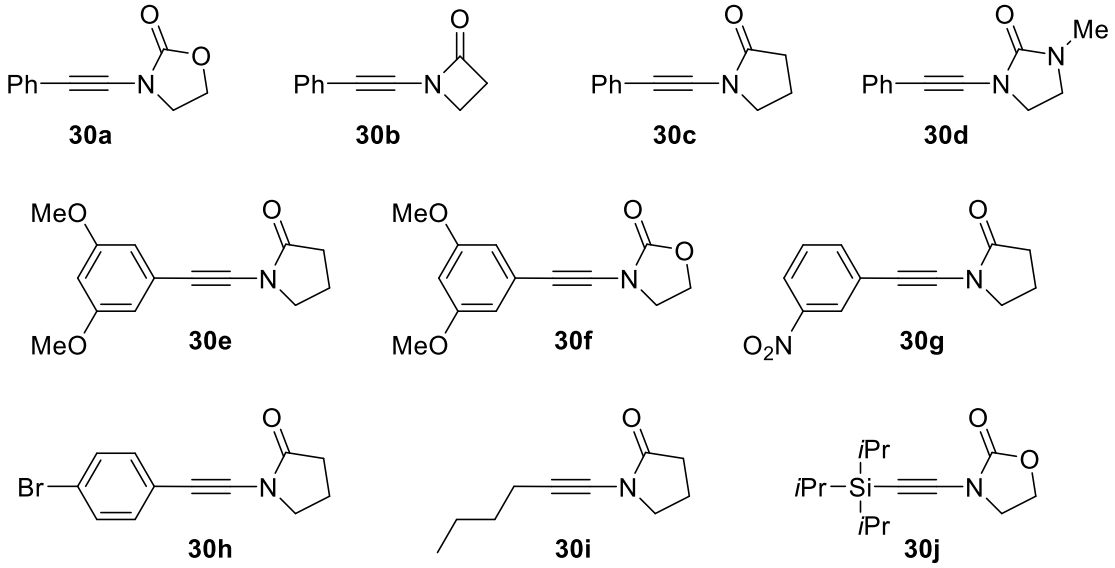
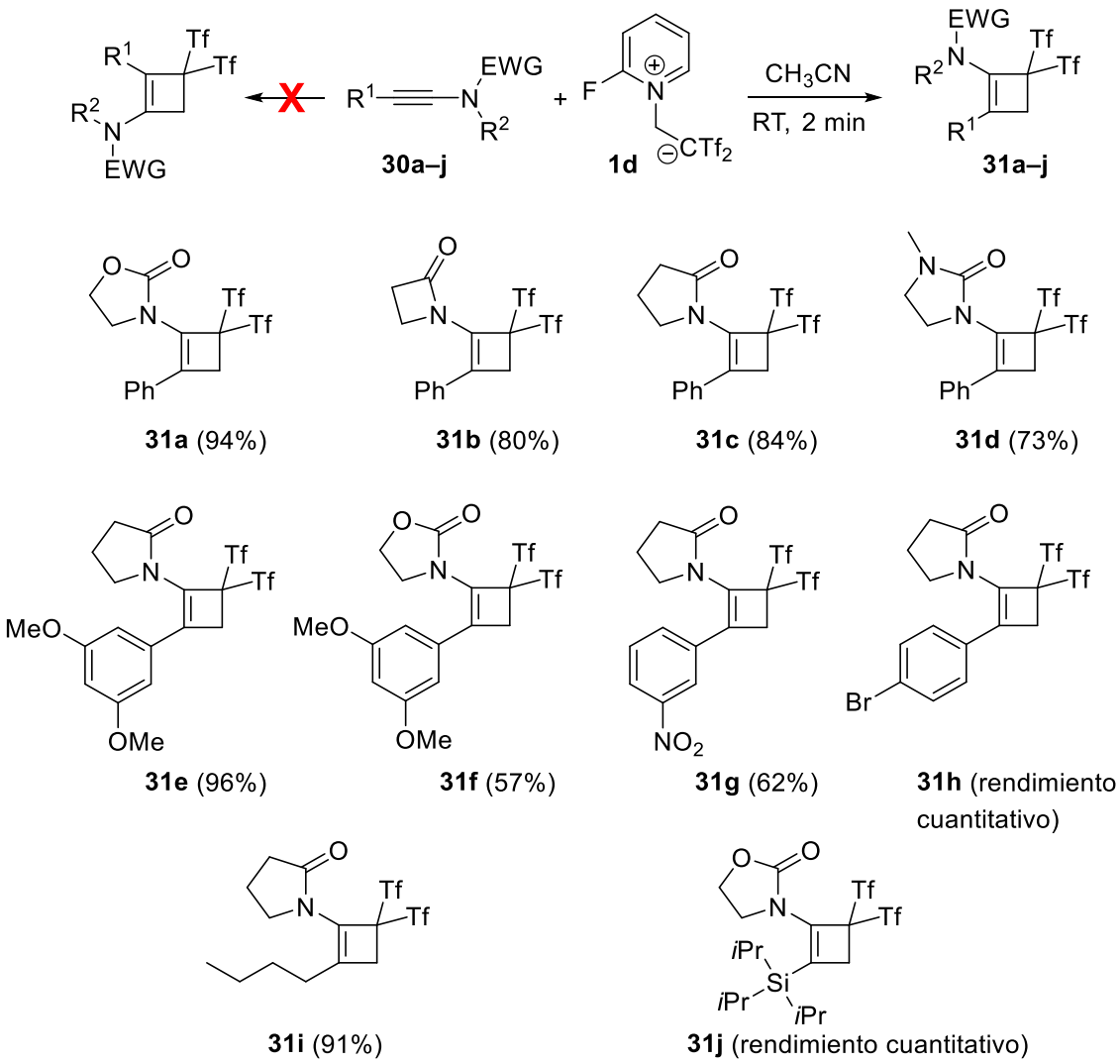


Figura XII.4

En este caso no se llevó a cabo un proceso de optimización de condiciones, pues las condiciones optimizadas anteriormente son totalmente válidas. Al tratar las inamidas **30a-j** con una cantidad equimolar del zwitterión **1d** en acetonitrilo a temperatura ambiente, se obtuvieron los ciclobutenos **31a-j** (Esquema XII.15).



Esquema XII.15

Los productos **31a-j** representan una colección de 4,4-bis(trifluorometanosulfonil)-ciclobut-1-enamidas que demuestra un buen alcance de la reacción, pues pese a los cambios estructurales, todas las reacciones transcurren de manera limpia, muy rápida, los rendimientos son en la mayoría de casos excelentes y la regioselectividad es total. Como ocurría en el Capítulo anterior con las inaminas, en este caso, el nitrógeno de las inamidas también dicta la formación de un único regioisómero.

El siguiente grupo de inamidas estudiado fueron aquellas en las que el triple enlace se encuentra activado con sustituyentes aromáticos que incorporan grupos electro-dadores (metoxilos) en posiciones *orto* y/o *para*. Estas son las inamidas **30k-v** (Figura XII.5).

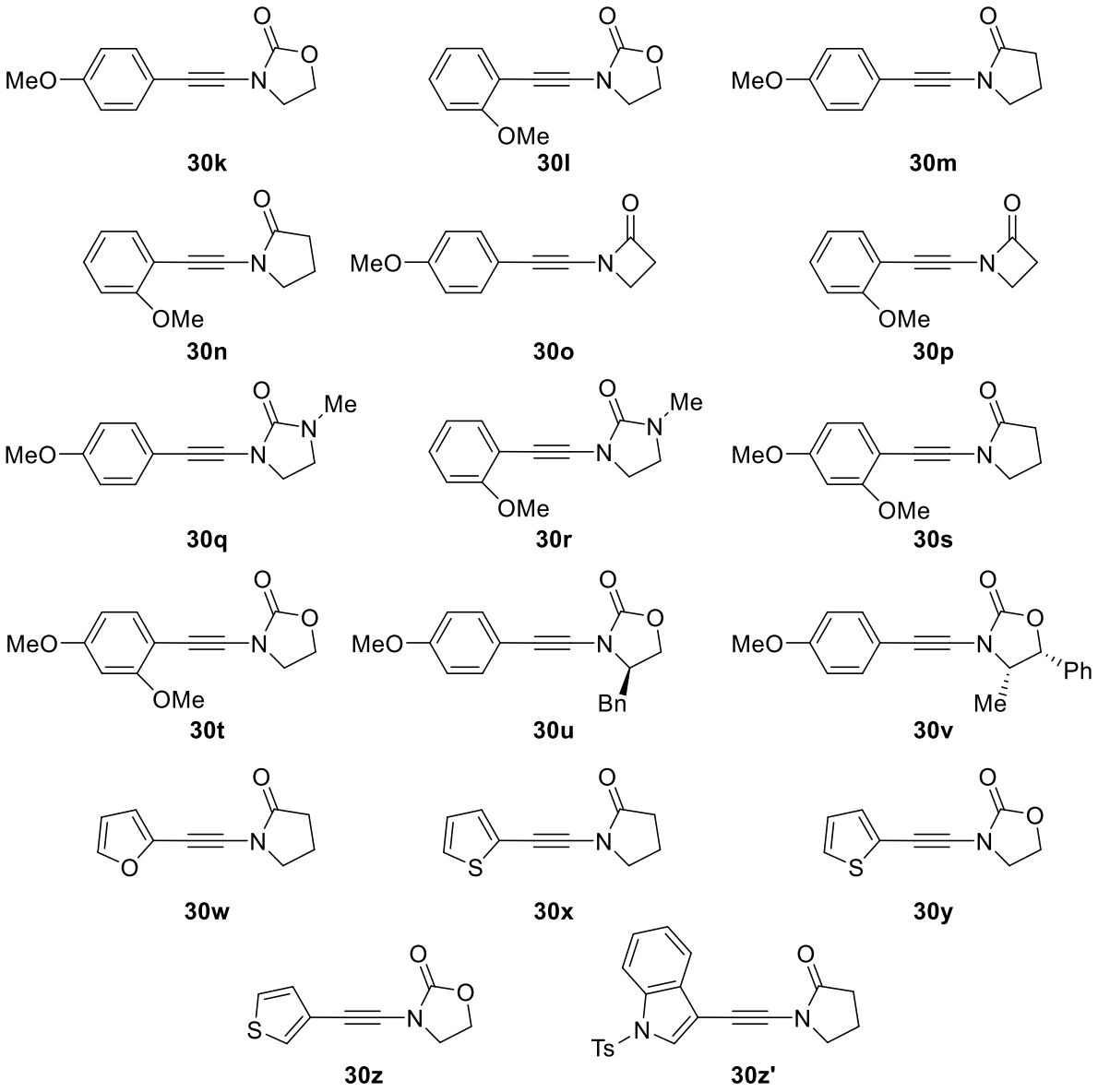
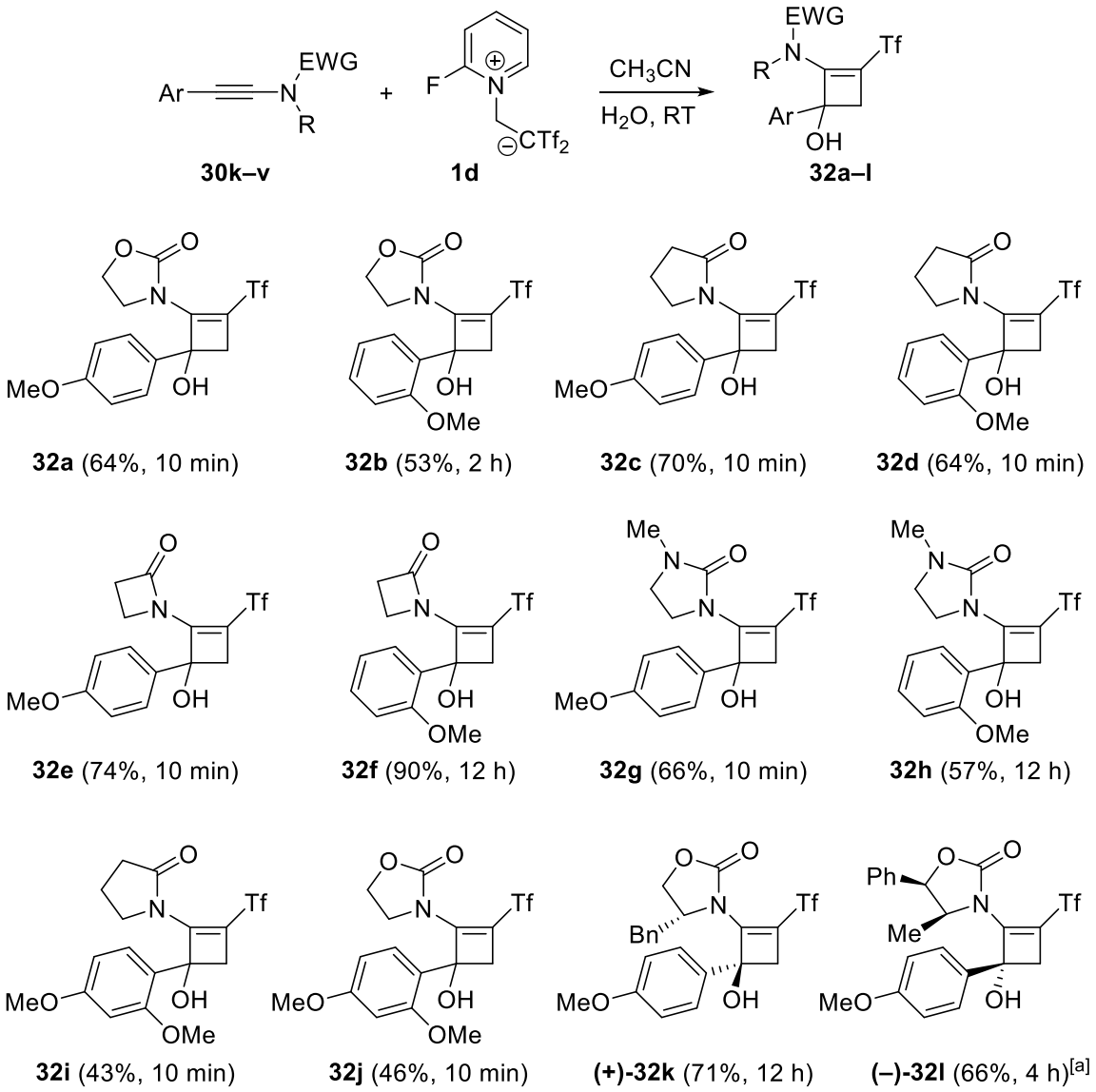


Figura XII.5

Cuando las inamidas **30k-v** se sometieron a las condiciones generales de reacción, se hizo patente el cambio provocado por el efecto electrónico de sus arilos activados, los cuales modifican la reactividad final originando los ciclobutenoles **32a-j** (Esquema XII.16). Aunque no se detecta la formación de los compuestos tipo **31** en este caso, posiblemente los ciclobutenos intermedios **31k-v** deben experimentar una reacción adicional. Es decir, las inamidas **30k-v** sufren una secuencia de ciclación/hidroxilación muy rápida, lo que impide detectar o aislar el intermedio tipo **31**.



[a] Se muestra el isómero mayoritario (r.d. = 80:20).

Esquema XII.16

La reacción también se escaló con éxito en el orden de gramos para la inamida **30p**, lo que demuestra la robustez de la metodología. Sin embargo, para las inamidas altamente activadas **30s** y **30t**, se detectó la formación de productos secundarios no determinados, lo cual, posiblemente, sea la causa del menor rendimiento en la formación de **32i** y **32j**. A pesar del impedimento estérico adicional que suponen los sustituyentes de las oxazolidinonas enantiopuras **30u** y **30v**, no es una traba en el transcurso de la reacción, pudiéndose obtener con buenos rendimientos los aductos **32k** (enantiopuro) y **32l** (mezcla diasteromérica, r.d. = 80:20).

Para asegurarnos completamente de la estructura de estos compuestos se realizó el análisis por difracción de rayos X de monocristal del producto **32a** (Figura XII.6).

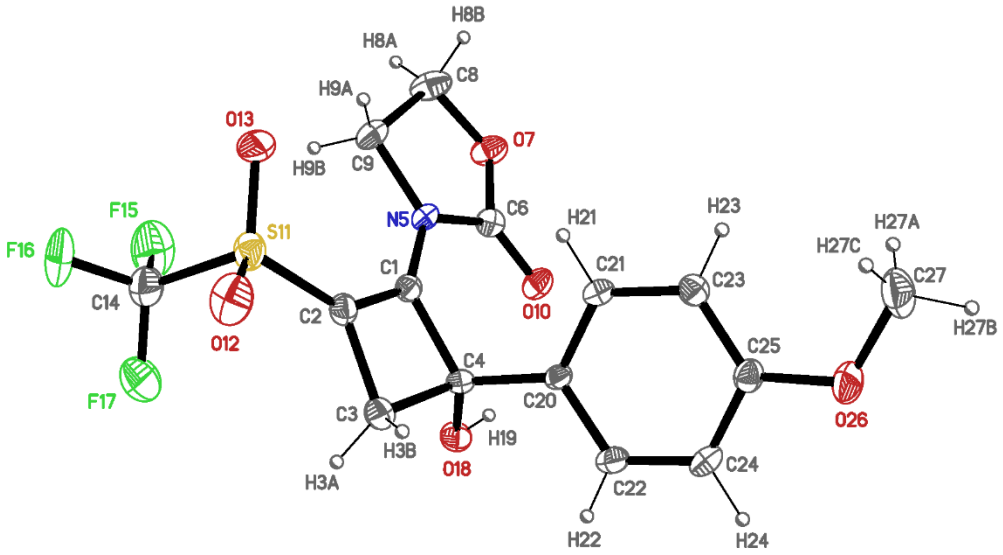
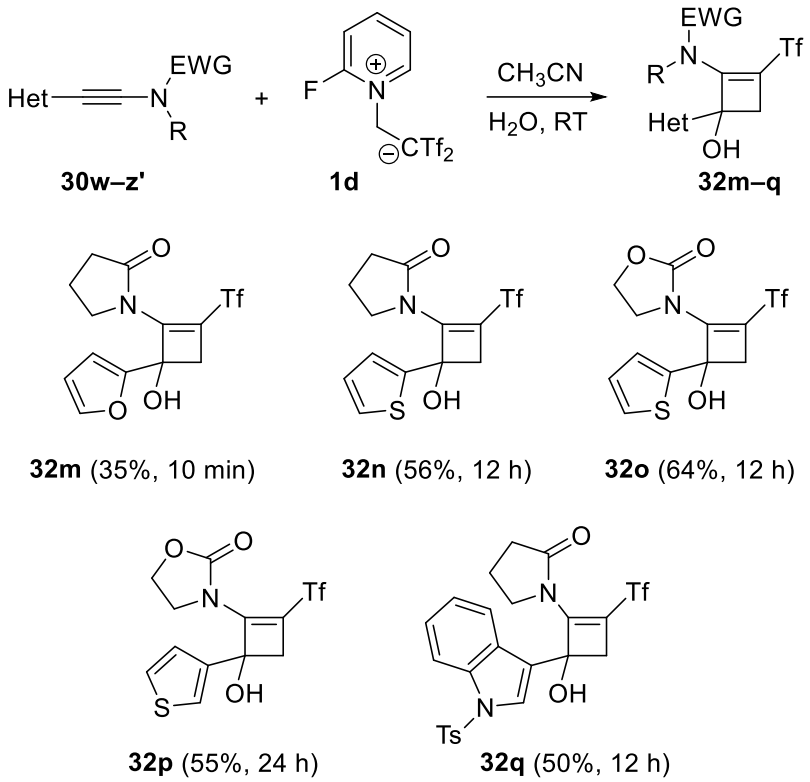


Figura XII.6

El hidroxilo incorporado a la estructura cíclica tiene que proceder del agua presente en el disolvente, así como de la humedad ambiental. Este hecho puede comprobarse experimentalmente ya que añadiendo 1.5 equivalentes de H_2O, se observa una aceleración del proceso con tiempos de reacción más cortos. Es importante señalar lo novedoso que resulta este protocolo, pues todos los métodos sintéticos conocidos hasta ahora para acceder a ciclobutenoles implican la reducción de ciclobutenonas.

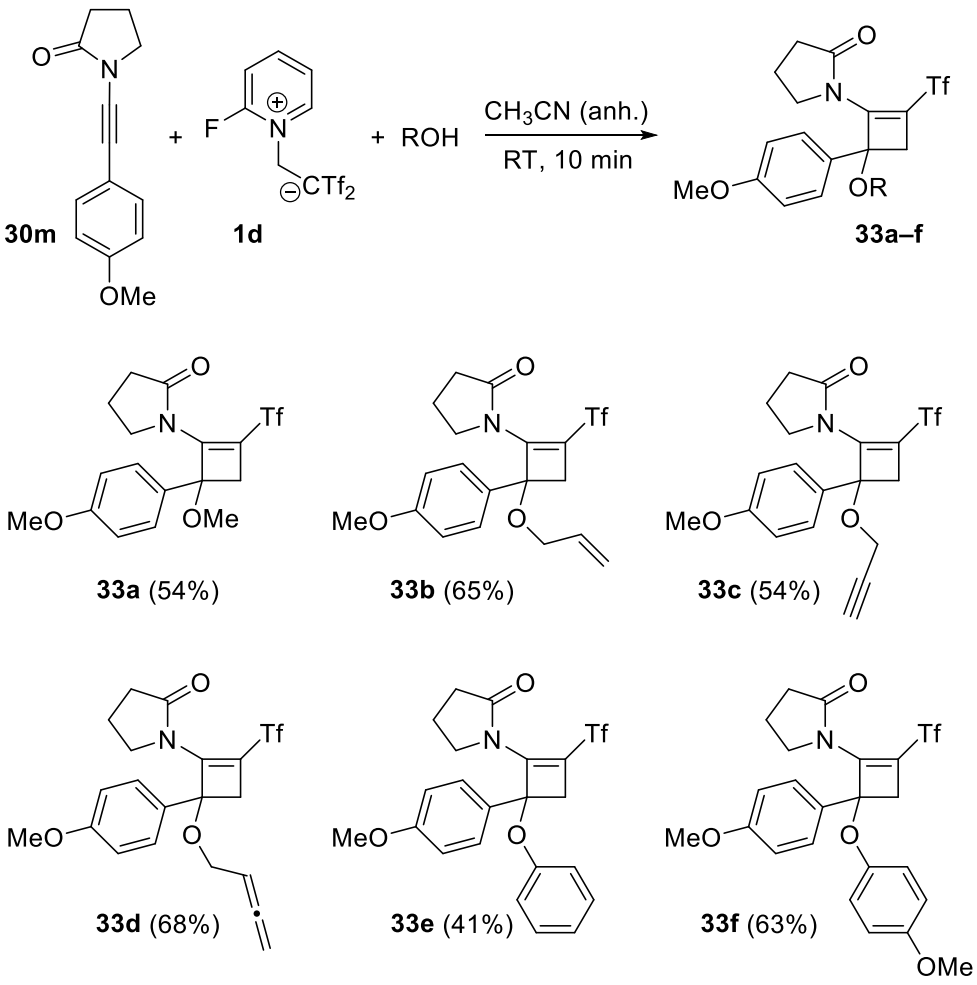
Intrigados si este comportamiento quedaba reducido a inamidas con arilos activados con metoxilos, se prepararon una nueva serie de inamidas **30w-z'**, también activadas, pero con heterociclos π-excedentes (Figura XII.5). Afortunadamente, aplicando las mismas condiciones de reacción, las inamidas **30w-z'** mostraron un comportamiento similar, dando lugar a los ciclobutenoles **32m-q** (Esquema XII.17).



Esquema XII.17

De nuevo los efectos electrónicos y no los estéricos son los que realmente controlan la reacción, pues una inamida tan voluminosa como **30z'** muestra la misma reactividad que inamidas portadoras de sustituyentes menos voluminosos.

Considerando que el agua entra en la molécula actuando como nucleófilo, nos planteamos la posibilidad de sustituirla por alcoholes, para así expandir la metodología y la variedad estructural obtenida. Se tomó la inamida **30m** como sustrato modelo, la cual se trató en las mismas condiciones de reacción, pero asegurando un medio estrictamente anhidro y adicionando 1.5 equivalentes del alcohol a introducir. Los alcoholes elegidos fueron metanol, alcohol alílico, alcohol propargílico, propa-1,2-dien-1-ol, fenol y *para*-metoxifenol; a partir de los cuales se obtuvieron los aminociclobutenil éteres **33a-f** (Esquema XII.18).



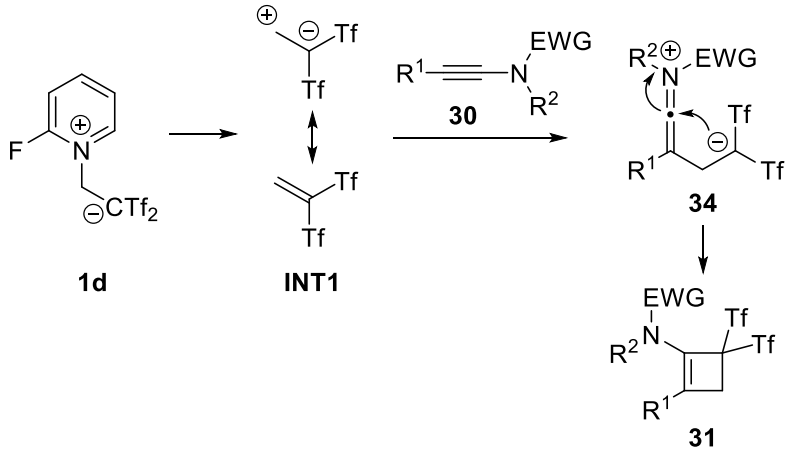
Esquema XII.18

Considerando la versatilidad de los grupos alqueno, alquino y aleno, los ciclobutenos **33b-d** resultan interesantes desde un punto de vista sintético para posteriores transformaciones. A pesar de la pobre nucleofilia que suelen mostrar los fenoles y los problemas de quimioselectividad que pueden originar, pues pueden reaccionar a través del átomo de O (del hidroxilo) o de un átomo de C (en las posiciones activadas del anillo), únicamente se obtienen los productos de hidroxilación **33e** y **33f**. En el caso de **33e**, también se observa la formación de un 10% del ciclobutenol **32c** pese a las condiciones anhidras. La alta afinidad por el agua de la inamida, unido al hecho de la menor reactividad del fenol, posibilitan su formación.

Un aspecto importante observado en los ciclobutenil éteres **33a-f** es que se pueden ser aislar y caracterizar, pero son inestables si los comparamos con los ciclobutenoles **32a-l**. La mayor estabilidad de los ciclobutenoles puede estar

relacionada con la formación de un enlace de hidrogeno entre O10···H19 observado en el análisis por difracción de rayos X del compuesto **32a**. Es decir, se establece entre el átomo de H del grupo hidroxilo y el átomo de O del grupo carbonilo un enlace que otorga rigidez y estabilidad a la estructura.

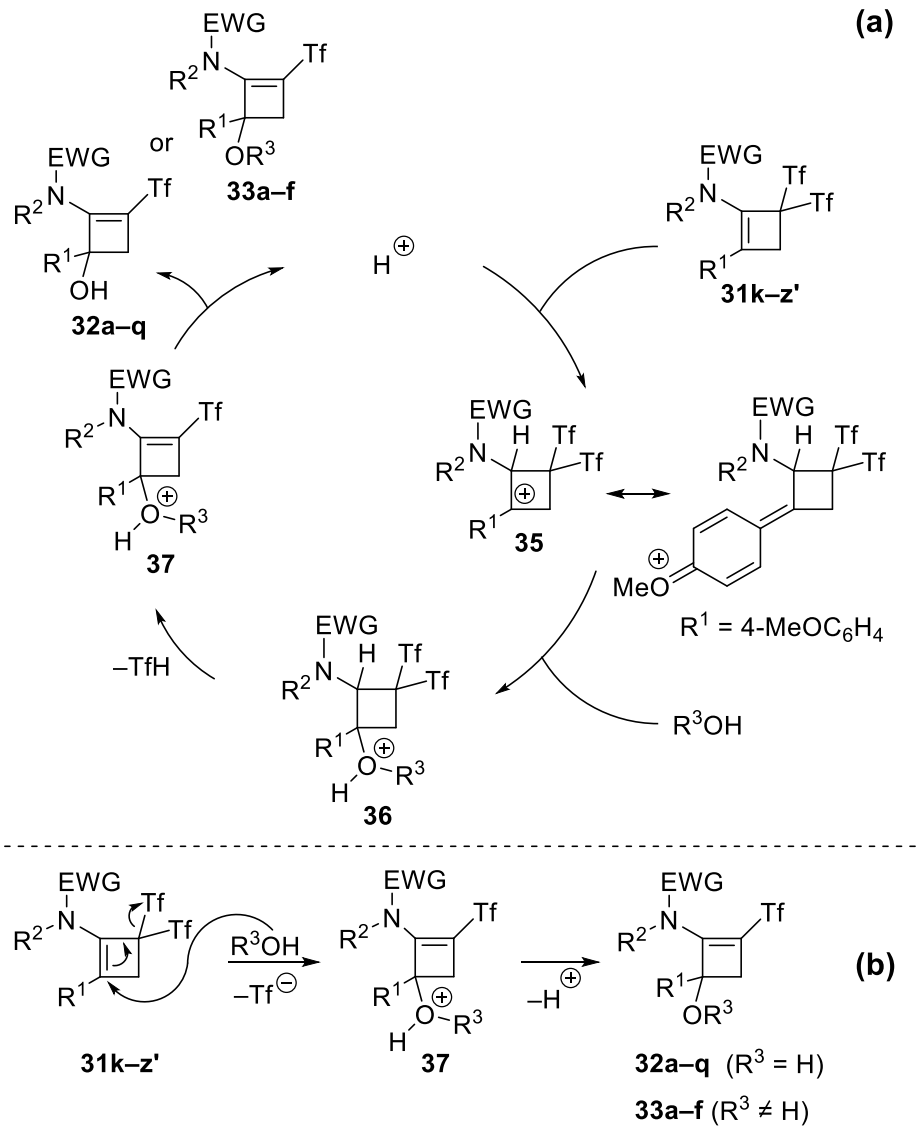
El mecanismo propuesto para la formación de los aminociclobutenos **31** por reacción entre la sal de 2-fluoropiridina **1d** y las inamidas **30** se muestra en el Esquema XII.19.



Esquema XII.19

Inicialmente, en disolución, se produce la liberación de la olefina altamente polarizada $Tf_2C{=}CH_2$ **INT1** que puede considerarse un híbrido de resonancia entre esta molécula neutra y el 1,2-dipolo. El siguiente paso es la reacción de cicloadición [2+2] entre las inamidas **30** y **INT1** generado *in situ*, conduciendo a la especie zwitteriónica **34**. Este producto de adición **34** inicia una reacción de cierre de anillo que conduce finalmente a la 4,4-bis(trifluorometanosulfonil)ciclobut-1-enamida **31**. El mecanismo es equivalente al propuesto en el Capítulo anterior para la reacción con inaminas. El regiocontrol de estas reacciones está originado por la estabilización dada por el grupo amida en el intermedio **34**, el cual anula el efecto de los otros sustituyentes.

Las propuestas mecanísticas para la formación de los ciclobutenoles **32** y los ciclobutenil éteres **33** se recogen en el Esquema XII.20.



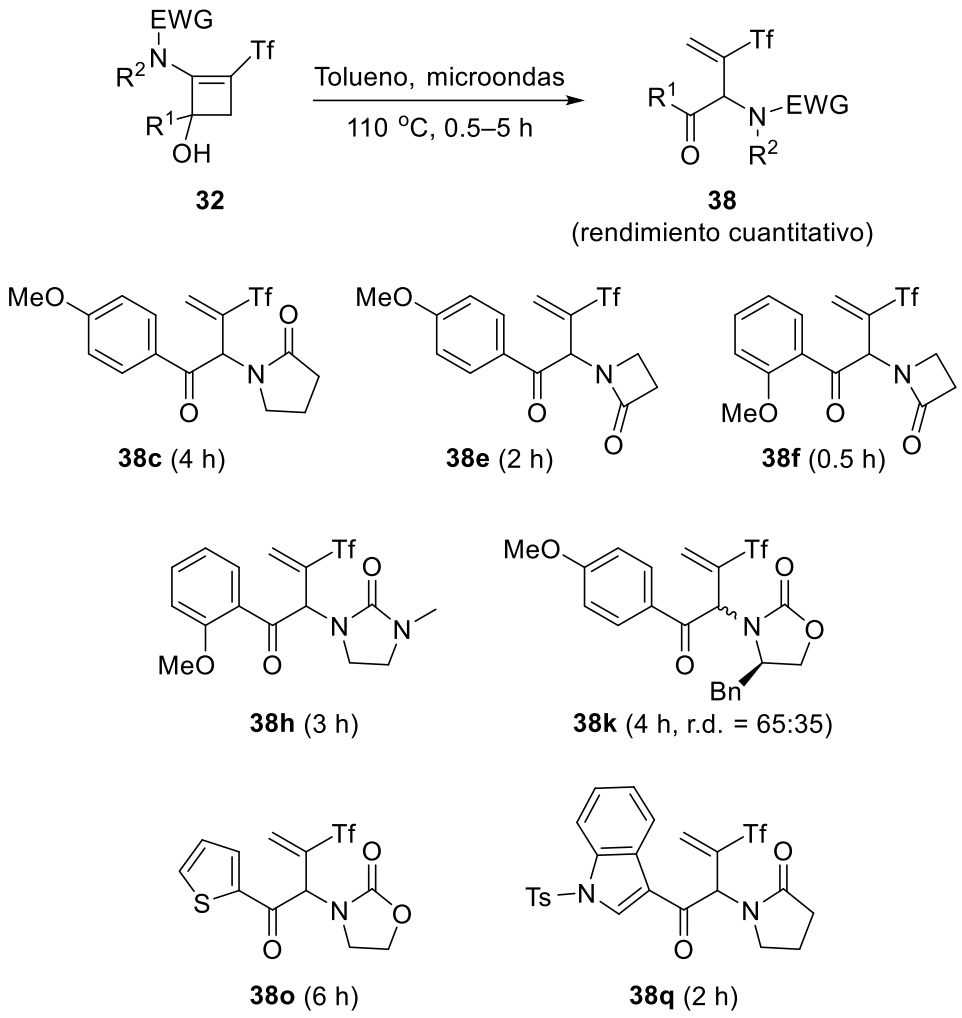
Esquema XII.20

El mecanismo para el caso de las inamidas activadas **30k-z'** implica un rápido ataque nucleófilo por parte del agua o los alcoholes, con la subsiguiente eliminación de TfH, que conduce a la formación de los productos **32** y **33**. La conversión de los aminociclobutenos del tipo **31** en los aductos **32** y **33** puede involucrar la formación inicial de los carbocationes **35** a través de la adición de un protón al doble enlace de las enamidas **31k-z'**. La fuerza impulsora de este proceso puede estar relacionada con la estabilización de la carga positiva de las especies **35** por los anillos ricos en electrones. Seguidamente, un ataque nucleófilo por parte del átomo de O (del agua o alcoholes) a la posición bencílica de las especies catiónicas **35**, conlleva la formación del catión oxonio **36**. La subsiguiente pérdida de TfH genera las especies

37, que evolucionan por pérdida de un protón y conducen a los productos finales **32** y **33**, regenerándose el catalizador en esta última etapa.

El tratamiento del ciclobuteno **31c** con agua y cantidades catalíticas de ácido (HCl, H_2SO_4 o TfOH) condujo a una mezcla compleja de reacción. Este resultado, unido a lo poco usual que resulta la protonación de enamidas en el carbono de la posición α, nos hizo proponer un mecanismo alternativo (Esquema XII.20, apartado b). Este implica el ataque nucleófilo directo del agua o alcoholes en la posición bencílica con la subsiguiente salida de Tf, generándose el intermedio **37**. Una pérdida final de protón conduciría a los productos finales **32** y **33**.

A continuación, centramos nuestra atención en la utilidad sintética que pueden ofrecer los productos obtenidos ya que la inherente tensión de anillo que presentan los ciclobutenos puede aprovecharse para producir transformaciones. La apertura de anillo de los ciclobutenoles **32** es posible cuando se calientan en tolueno a 110ºC en un reactor de microondas. Esta apertura da lugar a la formación de cetonas α-amino-β,γ-insaturadas **38** (Esquema XII.21). La reacción transcurre limpiamente, con rendimiento cuantitativo y sin necesidad de purificación. La oxazolidinona enantioenriquecida **38k** se forma como una mezcla diasteromérica (r.d. = 65:35) en el nuevo centro estereogénico generado. Hay que señalar que este método permite el acceso a cetonas α-amino-β,γ-insaturadas sin producirse isomerizaciones a cetonas α,β-insaturadas, problema común de los métodos tradicionales.



32 **38** (rendimiento cuantitativo)

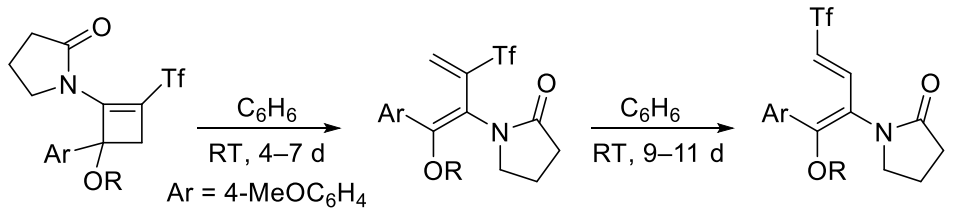
38c (4 h) **38e** (2 h) **38f** (0.5 h)

38h (3 h) **38k** (4 h, r.d. = 65:35)

38o (6 h) **38q** (2 h)

Esquema XII.21

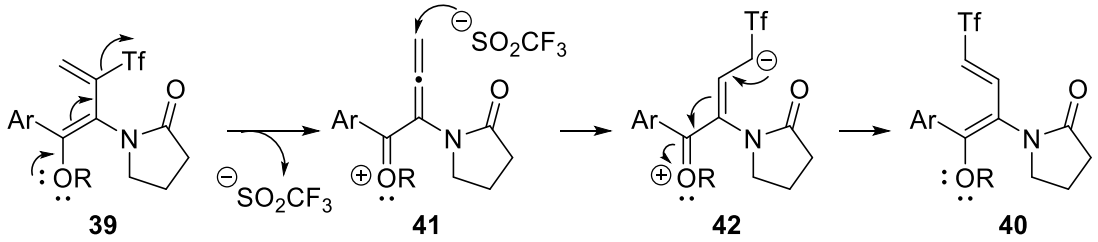
Aplicamos la misma estrategia de apertura de anillo para obtener productos derivados de los aductos **33**. Como se ha comentado anteriormente, los ciclobutenil éteres **33a-f** son relativamente inestables y si se dejan el tiempo suficiente en disolución de benceno a temperatura ambiente se produce la apertura 4π-electrocíclica, que conduce a los (*Z*)-1,3-butadienos **39a-f**, en general, con buen rendimiento y total estereoselectividad (Esquema XII.22). Al tratarse de condiciones realmente suaves permiten trabajar con el compuesto **33d**, que posee un aleno sensible en su estructura, sin ningún tipo de problema.



33a R = metilo	**39a** (75%)	
33b R = prop-2-enilo	**39b** (cuantitativo)	
33c R = prop-2-inilo	**39c** (57%)	**40c** (51%)
33d R = buta-2,3-dienilo	**39d** (cuantitativo)	**40d** (38%)
33e R = fenilo	**39e** (53%)	**40e** (67%)
33f R = 4-metoxifenilo	**39f** (48%)	**40f** (64%)

Esquema XII.22

Sorprendentemente, descubrimos que si los dienos **39c-f** permanecen disueltos en benceno tiempos prolongados, siguen evolucionando hacia los (1*Z*,3*E*)-butadienos **40c-f** (Esquema XII.22). Esta conversión implica una migración espontánea no catalizada de grupo triflilo. Para explicar la transformación de **39** en **40** debemos apoyarnos en el hecho de que los grupos sulfona pueden actuar tanto de grupo saliente como de nucleófilo. El paso crítico del mecanismo es la eliminación del anión trifluorometanosulfonilo, lo que provoca la formación de la alenamida intermedia **41** (Esquema XII.23). A continuación, la adición nucleófila de este anión trifluorometanosulfonilo en el carbono terminal del aleno **41** genera la especie zwitteriónica **42** que, tras un reagrupamiento, origina las triflonas finales **40**.



Esquema XII.23

Desgraciadamente, los sustratos **39a** y **39b** no evolucionan hacia los (1*Z*,3*E*)-butadienos **40** correspondientes, originándose en su lugar una mezcla compleja de productos.

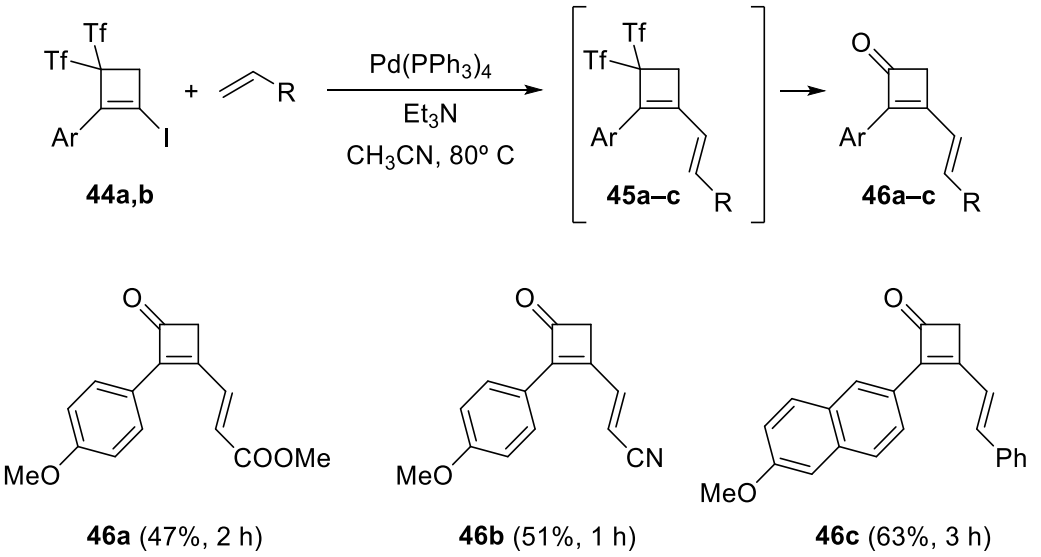
XII.1.4. Síntesis de ciclobutenonas 2,3-disustituidas en condiciones de acoplamiento cruzado catalizado por paladio. Aplicaciones sintéticas

Una vez explorada la reactividad sobre alquinos sustituidos por heteroátomos decidimos encontrar alguna transformación interesante para los ciclobutenos obtenidos. Centramos nuestra atención sobre los halociclobutenos del Capítulo 2, dado que al ser portadores de la funcionalidad C(sp^2)−X (X = Cl, Br ó I) eran susceptibles de reaccionar en condiciones de acoplamiento cruzado catalizadas por paladio.

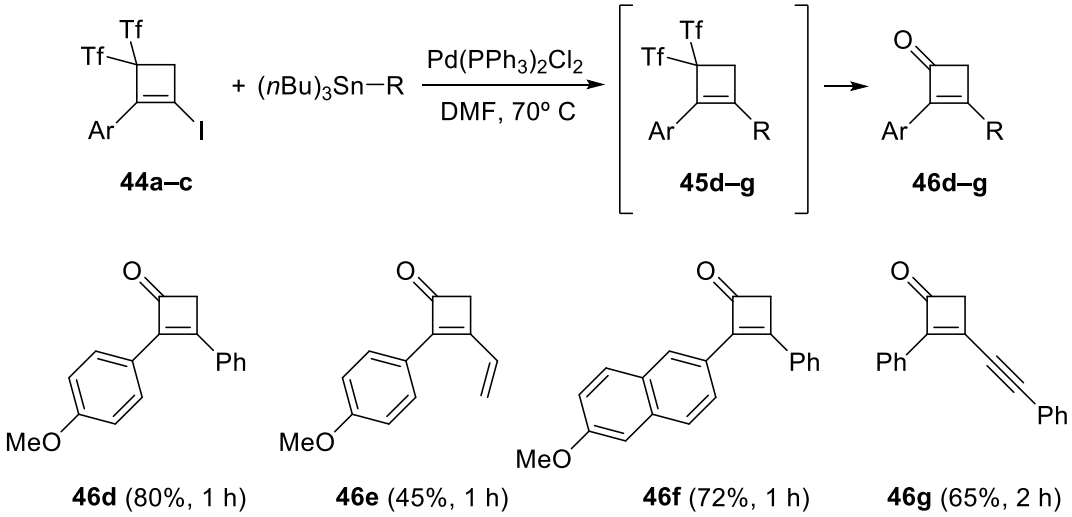
Las reacciones de acoplamiento cruzado pueden considerarse como uno de los grupos de reacciones más importante de la Química Orgánica. La posibilidad de formar nuevos enlaces C−C de manera sencilla sobre sustratos inusuales, como son los ciclobutenos, nos abría la posibilidad de funcionalizar el anillo regioselectivamente y multiplicar así su interés y utilidad.

Al ser procesos ampliamente estudiados desde hace años, es un hecho contrastado que los sustratos yodados son, en general, más reactivos que sus equivalentes bromados y clorados. Por ello decidimos emplear directamente yodociclobutenos en nuestro estudio.

El primer acoplamiento cruzado ensayado sobre los sustratos **44** fue en condiciones de Negishi. Desafortunadamente, no se observaron cambios en el material de partida, recuperándose los yodociclobutenos inalterados. Sin embargo, cuando se aplicaron a estos mismos sustratos **44** condiciones Heck y Stille el acoplamiento se alcanzó satisfactoriamente. Sorprendentemente, no se aislaron los ciclobutenos esperados **45a-c** y **45d-g**, sino los originados de la hidratación del anillo y pérdida de los dos grupos Tf tras el acoplamiento cruzado. Esta hidratación provoca la transformación del carbono que soporta el grupo *gem*-bis(triflilo) en un carbono carbonílico, obteniéndose como producto final las ciclobutenonas **46a-c** en condiciones Heck (Esquema XII.24) y las ciclobutenonas **46d-g** en condiciones Stille (Esquema XII.25).

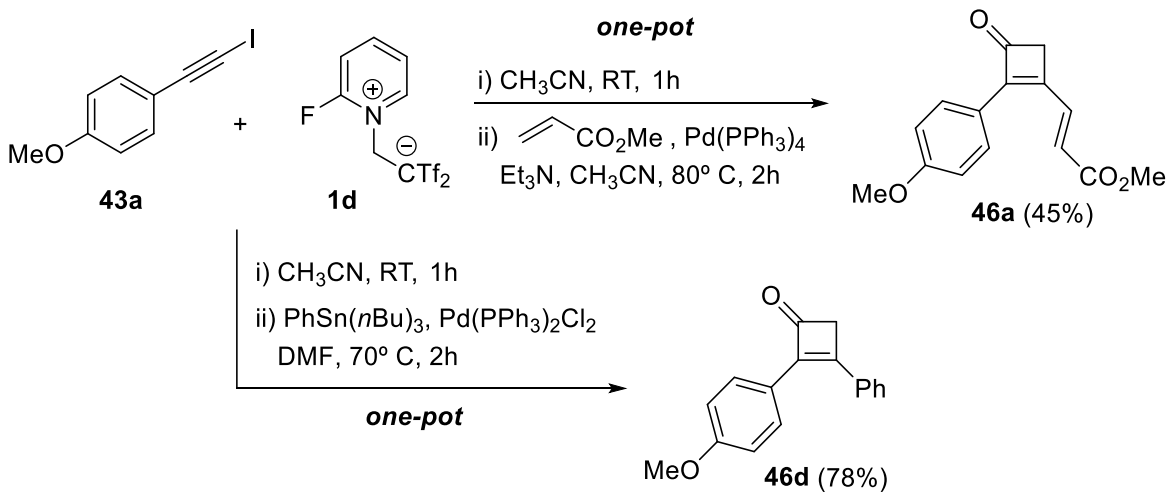


Esquema XII.24



Esquema XII.25

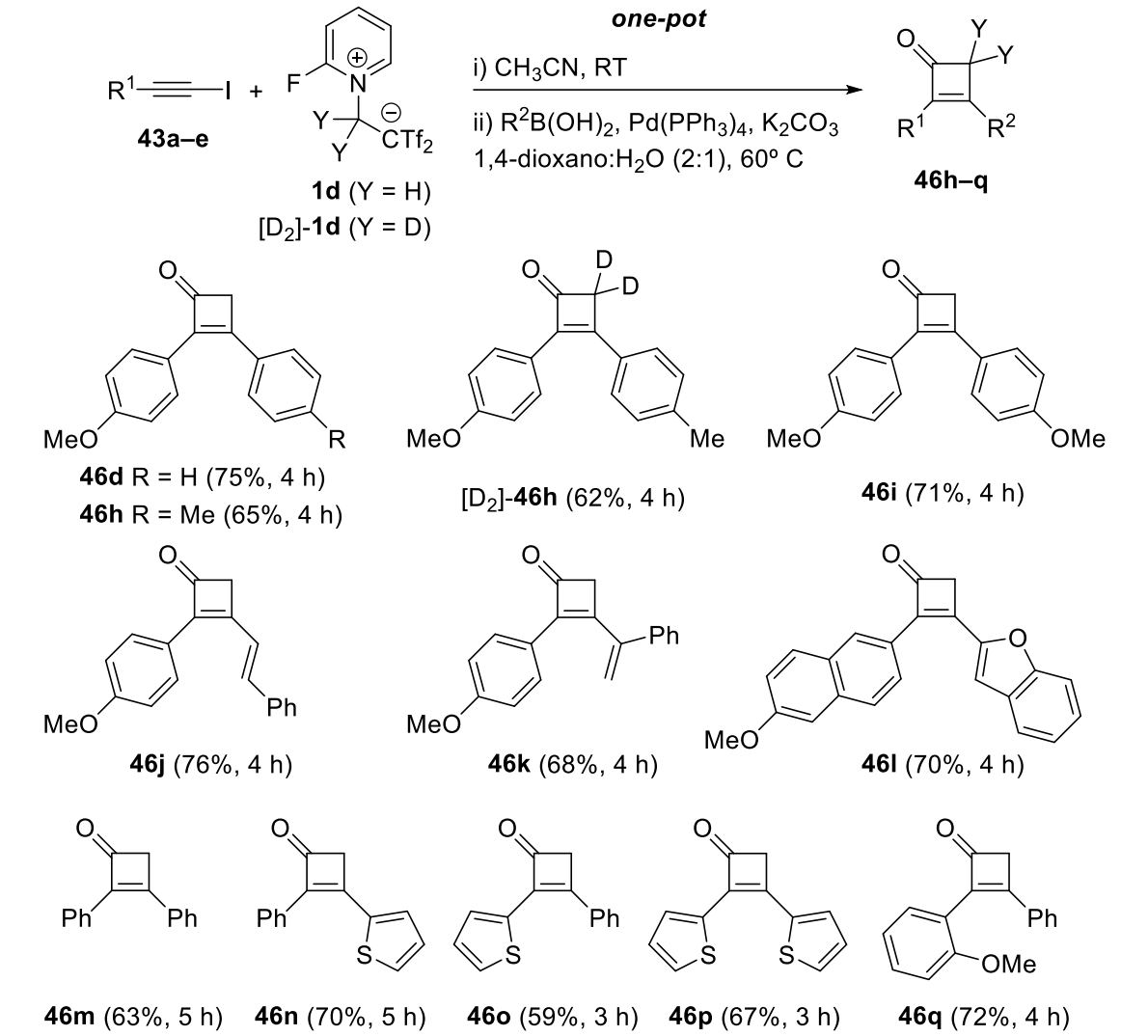
Dado que las reacciones de formación de los yodociclobutenos de partida son realmente limpias, pensamos que sería una buena idea aprovechar esta característica para diseñar un protocolo de síntesis de ciclobutenonas en un solo paso (*one-pot*) desde yodoalquinos. Así, los crudos resultantes del tratamiento de los yodoalquinos **43** con la sal de 2-fluoropiridinio **1d**, previa eliminación del disolvente acetonitrilo por destilación a vacío, se trataron en las condiciones Heck y Stille anteriores. Satisfactoriamente, se obtuvieron las ciclobutenonas esperadas **46a** y **46d** (Esquema XII.26), demostrando que el protocolo en un paso es una alternativa válida en estos procesos.



Esquema XII.26

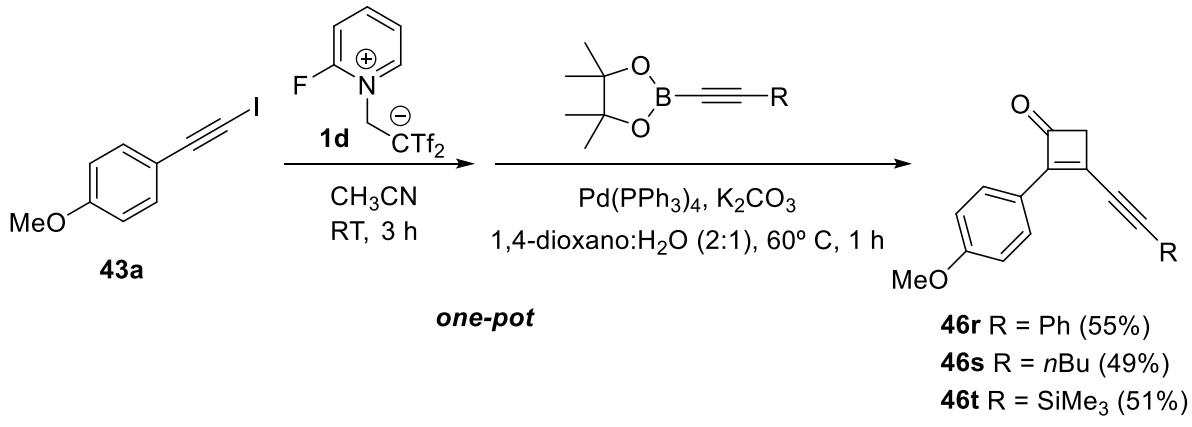
Con el conocimiento adquirido, creímos conveniente extender la metodología *one-pot* en condiciones de Suzuki. Las condiciones de reacción propias de este tipo de acoplamiento fueron previstas como muy favorables, ya que el uso de agua en el medio de reacción favorecería la formación del grupo carbonilo. Además, estas condiciones son más suaves y la disponibilidad comercial de ácidos y ésteres borónicos diversos es bastante superior a la de alquenos monosustituidos y estannanos. También es importante señalar la baja toxicidad que presentan los compuestos de boro respecto a aquellos que contienen estaño en su estructura.

De esta manera, partiendo de diferentes yodoalquinos **43** y del zwitterión **1d**, del correspondiente ácido borónico, catalizador de paladio, carbonato potásico como base, una mezcla 2:1 de 1,4-dioxano:H_2O como disolvente y calentando a 60ºC conseguimos sintetizar las diferentes ciclobutenonas 2,3-difuncionalizadas **46h-q** con moderados o buenos rendimientos (Esquema XII.27). La metodología permite el acceso directo a ciclobutenonas con total regioselectividad, desde unos materiales de partida fácilmente accesibles como son los yodoalquinos y sin necesidad de aislar ningún producto intermedio.



Esquema XII.27

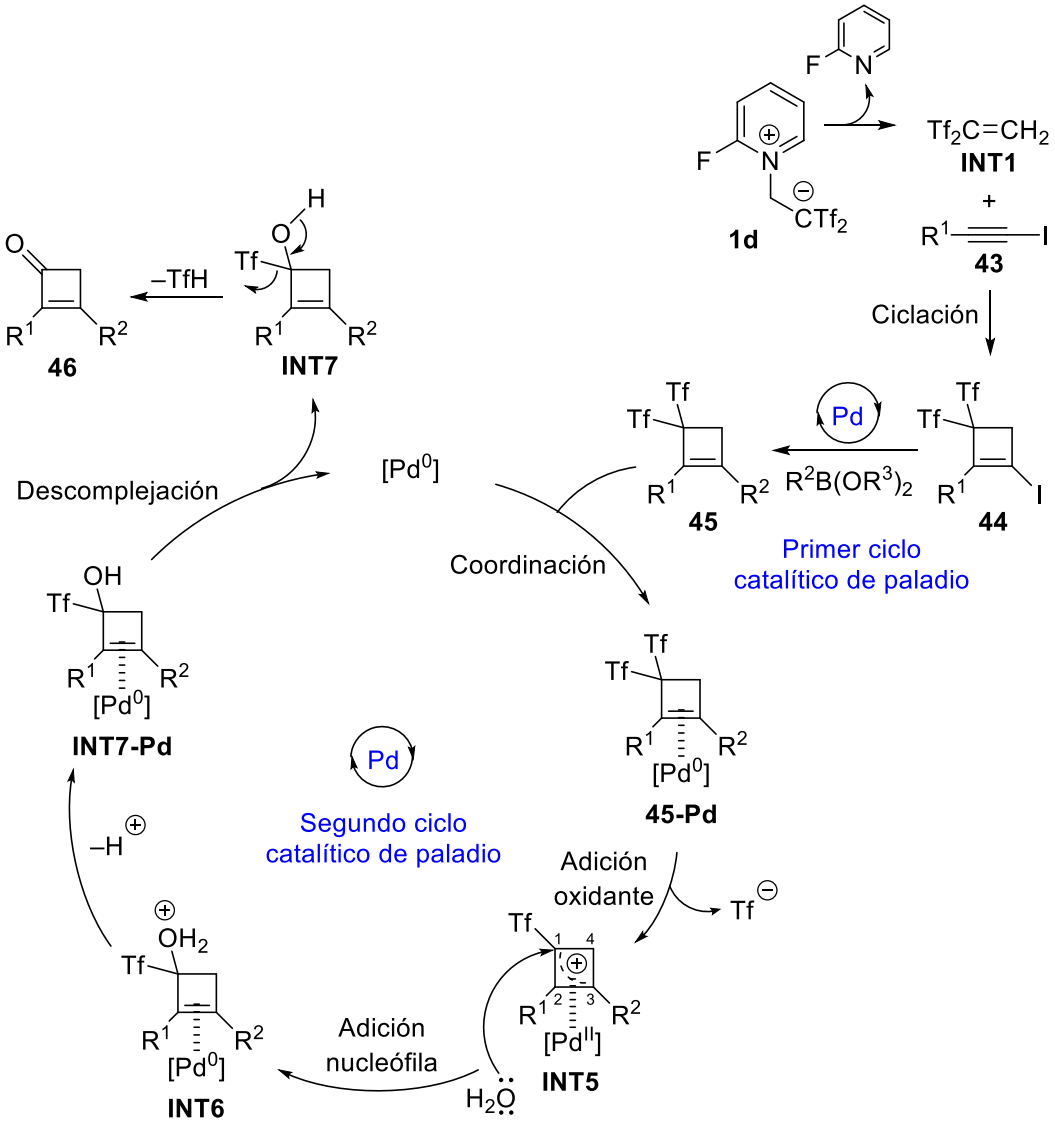
La metodología también funciona con los pinacolésteres alquinilborónicos con sustituyentes de diferente naturaleza (Esquema XII.28).



Esquema XII.28

Este protocolo simple y en un solo paso ha demostrado ser válido para la obtención de 2,3-diaril-ciclobutenonas, 2-aril-3-alquinil-ciclobutenonas y 2-aril-2-alquenil-ciclobutenonas. También hemos demostrado la posibilidad de obtener la versión deuterada de estas ciclobutenonas a través del ejemplo [D_2]-**46h** (Esquema XII.27).

En el Esquema XII.29 se muestra una propuesta mecanística para los procesos involucrados.

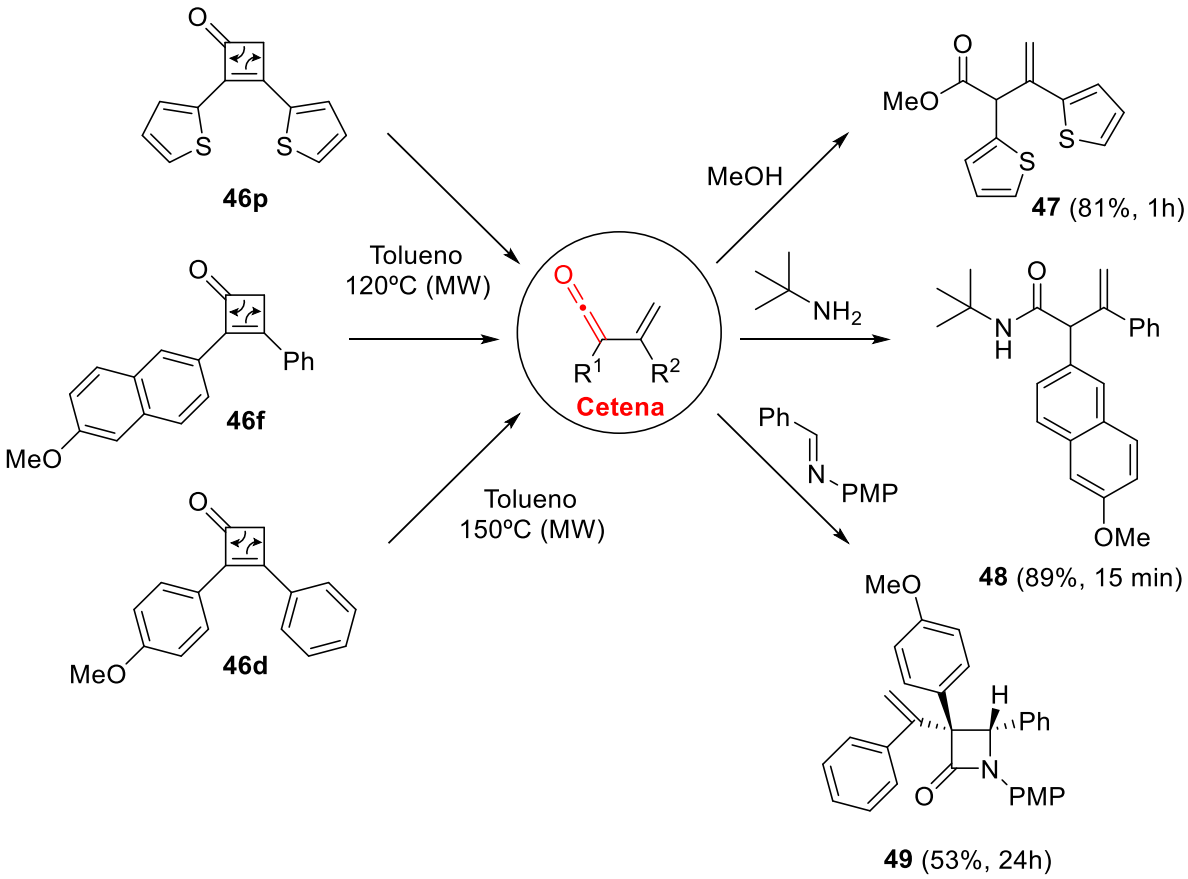


Esquema XII.29

En primer lugar, los yodoalquinos **43** se convierten en los bis(triflil)yodociclobutenos **44** por reacción con la molécula de $Tf_2C{=}CH_2$ generada *in situ.* Los aductos **44** reaccionan con los ácidos o ésteres borónicos en presencia

del catalizador de paladio en una reacción clásica de acoplamiento cruzado, completando el primer ciclo catalítico y formándose los bis(triflil)ciclobutenos **45**. A continuación, los productos **45** se incorporan al segundo ciclo catalítico por coordinación del doble enlace al catalizador de Pd^0, dando la especie **45-Pd**. Después de la coordinación, el catalizador promueve la adición oxidante de los sustratos alílicos **45**, con salida de un grupo Tf y generándose en el proceso la especie de π-alil-paladio **INT5**. Las especies **INT5**, en las que el paladio se ha oxidado de Pd^0 a Pd^{II}, son muy reactivas y sufren el ataque nucleófilo de una molécula de H_2O en la posición 1 originando los intermedios **INT6** y reduciéndose el paladio a su estado de oxidación original Pd^0. Tras una desprotonación del catión oxonio **INT6**, que origina las especies **INT7-Pd**, se produce la descoordinación del paladio. En este paso se liberan los ciclobutenoles **INT7** y se regenera el catalizador. Finalmente, los aductos **INT7** pierden el segundo grupo Tf en forma de TfH para dar las ciclobutenonas **46** como producto final.

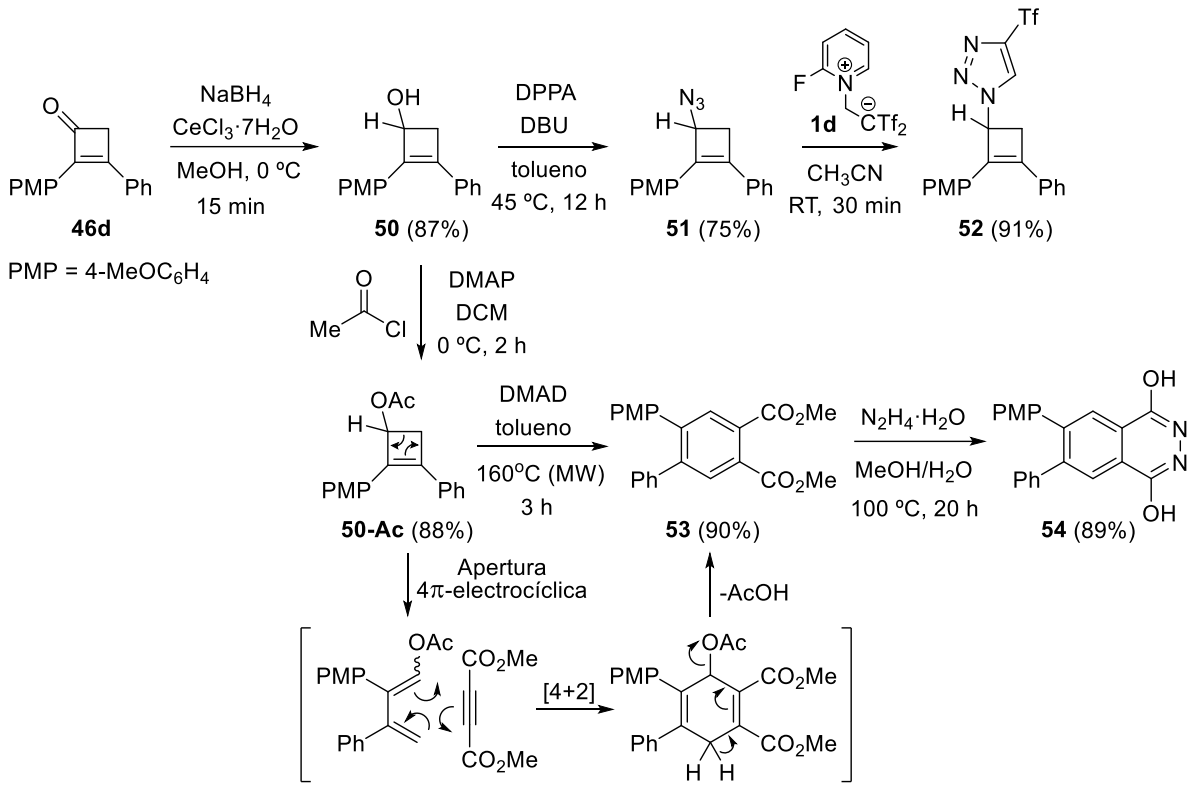
Para mostrar la utilidad sintética que poseen las ciclobutenonas y en consecuencia de la metodología que hemos desarrollado para su obtención, decidimos llevar a cabo una serie de transformaciones para los carbociclos **46**. Las primeras transformaciones que probamos se basan en aprovechar la inherente tensión de anillo de estos sistemas. La apertura electrocíclica por vía térmica forma cetenas, grupo funcional muy reactivo que puede ser atrapado *in situ* mediante el ataque de un nucleófilo, en nuestro caso un alcohol o amina, o bien con grupos funcionales insaturados para lograr cicloadiciones, en nuestro caso una imina (Esquema XII.30).



Esquema XII.30

Cuando la ciclobutenona **46p** se calentó a 120ºC en reactor microondas en presencia de metanol se obtuvo el ester β,γ-insaturado **47** con un 81% de rendimiento. De manera análoga, cuando al sustrato **46f** le aplicamos las mismas condiciones de reacción pero en presencia de *terc*-butilamina se obtuvo la amida β,γ-insaturada **48** con un 89% de rendimiento. Empleando unas condiciones más enérgicas y con tiempos de reacción más prolongados, pudimos transformar la ciclobutenona **46d** en la β-lactama **49** con un 53% de rendimiento por reacción de Staudinger con la imina *N*-(4-metoxifenil)-1-fenilmetanimina. En este último ensayo hay que destacar que la β-lactama **49** se obtuvo con total estereoselectividad.

Las siguientes transformaciones exploradas se centraron en la modificación previa del grupo carbonilo de las ciclobutenonas. Se tomó la ciclobutenona **46d** como modelo y se redujo selectivamente, sin afectar al doble enlace, mediante el uso de borohidruro sódico en presencia de tricloruro de cerio. Esta reducción permitió acceder al ciclobutenol **50** con un alto rendimiento (Esquema XII.31).

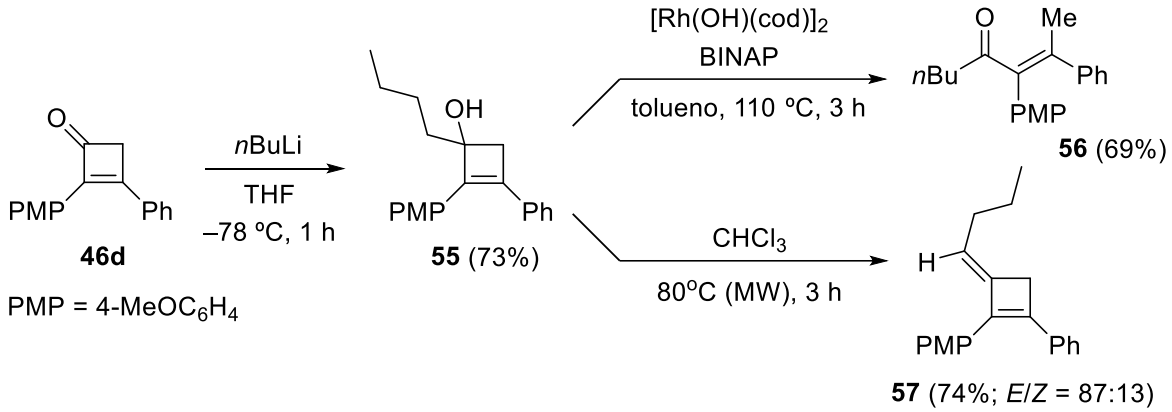


Esquema XII.31

El ciclobutenol **50** se convierte ahora en el material de partida para dos rutas diferentes. En la primera, el hidroxilo es sustituido por el grupo azida mediante el uso de difenilfosforil azida, lo que permite obtener el aducto **51** con buen rendimiento. Finalmente, se obtiene el ciclobutenil-triazol **52** por cicloadición formal [3+2] entre el grupo azida y la molécula $Tf_2C{=}CH_2$ generada a partir del zwitterión **1d**. Conviene recordar que la reacción de formación de este tipo de triazoles será estudiada en detalle en el último Capítulo de esta Discusión General.

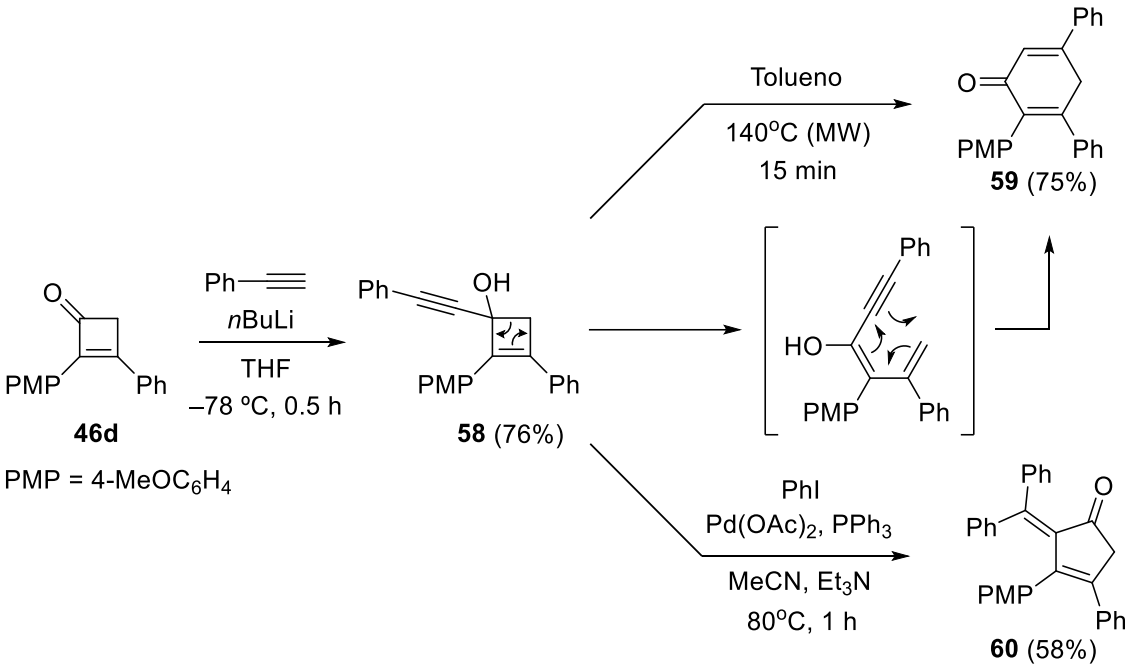
Una ruta sintética alternativa partiendo desde el ciclobutenol **50** permite acceder a la ftalazina **54**. Para alcanzar esta estructura son necesarias dos etapas previas, ya que inicialmente se produce la acetilación del grupo hidroxilo con cloruro de acetilo originando el acetato **50-Ac**. Cuando **50-Ac** se calentó en tolueno a 160ºC utilizando reactor microondas en presencia del alquino DMAD, se produjo la expansión de anillo por apertura electrocíclica del ciclobuteno y posterior cicloadición [4+2] con el alquino. El hexadieno cíclico generado experimenta aromatización por perdida de ácido acético (AcOH), originando el benceno tetrasustituido **53**. Finalmente, el tratamiento de **53** con hidracina en una mezcla metanol/agua origina la 1,4-diol-ftalazina-6,7-disustituida **54** con excelente rendimiento.

Exploramos también la adición de reactivos organometálicos para producir transformaciones de los productos originados. Al utilizar *n*BuLi sobre la ciclobutenona **6d** se obtuvo el ciclobutenol cuaternario **55**. A partir de este producto se sintetizó selectivamente el isómero *Z* de la cetona α,β-insaturada **56** mediante una apertura de anillo catalizada por rodio. También se logró la deshidratación del ciclobutenol **55** por simple calentamiento en cloroformo a 80ºC, lo que origina el ciclobutadieno **57** (Esquema XII.32).



Esquema XII.32

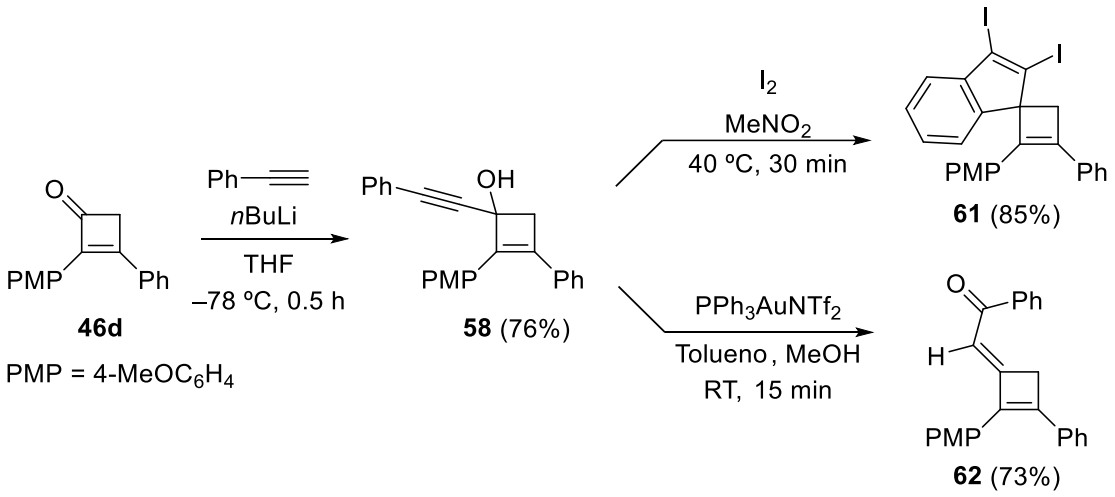
Si en lugar de usar *n*BuLi como nucleófilo en la reacción con la ciclobutenona **46d** utilizamos fenilacetiluro de litio obtenemos otro tipo de ciclobutenol, el alquinilciclobutenol **58**. Con la introducción de un alquino en el anillo de cuatro eslabones se abre la posibilidad de diversificar las estructuras derivadas de las ciclobutenonas. Las dos primeras transformaciones realizadas sobre el alquinilciclobutenol **58** implican una expansion de anillo (Esquema XII.33).



Esquema XII.33

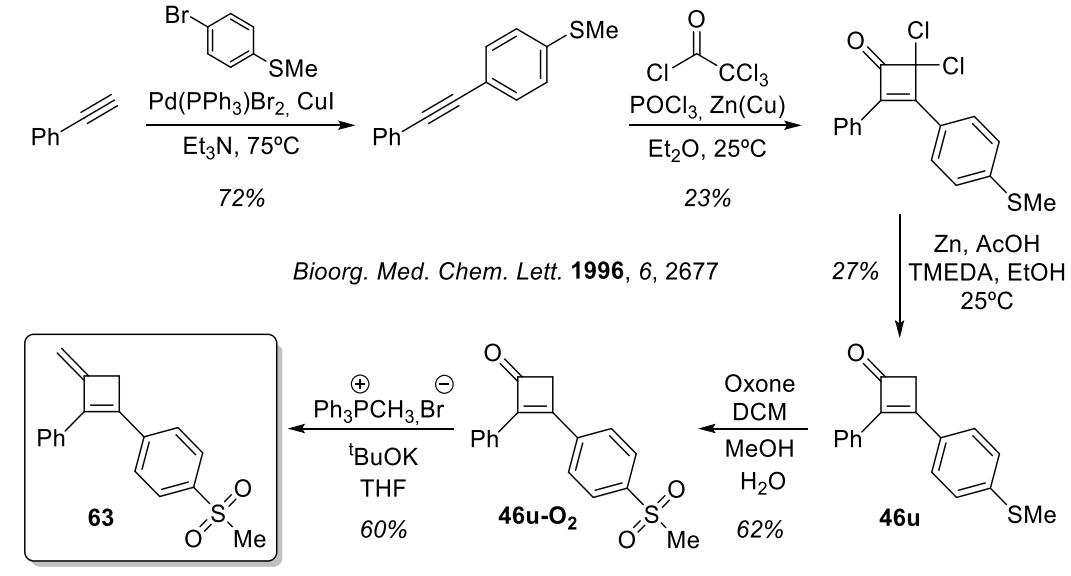
Por simple calentamiento del compuesto **58** a 140ºC en reactor microondas se consigue la expansión de anillo por apertura y cierre electrocíclico, generándose la 2,5-hexadienona **59** con buen rendimiento. Otra expansión de anillo, esta vez catalizada por paladio y acompañada por acoplamiento cruzado con yodobenceno nos permitió obtener la ciclopentenona **60** con rendimiento moderado.

Otras dos transformaciones sobre el alquinilciclobutenol **58**, sin expansión de anillo, nos permitieron obtener el ciclobuteno espirocíclico **61** mediado por yodo y la cetona α,β-insaturada **62** por reagrupamiento Meyer-Schuster catalizado por oro. En esta última transformación se obtuvo selectivamente el isómero *E* como único producto (Esquema XII.34).



Esquema XII.34

Como último reto dentro de este trabajo, nos propusimos la aplicación de la metodología desarrollada para la preparación de productos bioactivos. Tras una búsqueda exhaustiva en la bibliografía encontramos que algunas bis-aril-ciclobutenonas y estructuras derivadas presentaban actividad como inhibidores selectivos de la proteína ciclooxigenasa II (COX-II). En el Esquema XII.35 se muestra la ruta sintética original descrita en la literatura para la obtención de estas dianas.



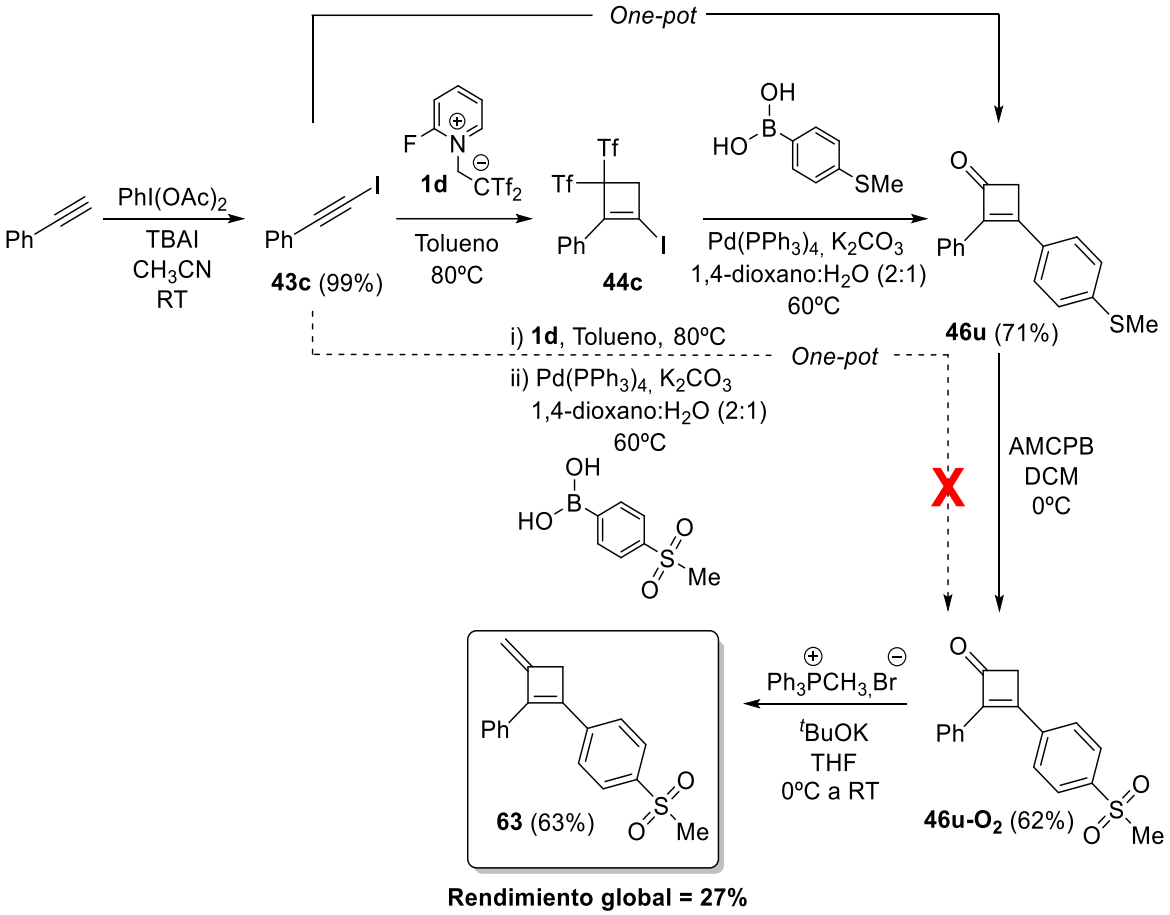
Rendimiento global = 1.7%

(COX-2) IC_{50}(μM) = 0.0012 (COX-2) IC_{50}(μM) = 0.11

(COX-1) IC_{50}(μM) = 0.54 (COX-1) IC_{50}(μM) = 4.4

Esquema XII.35

La ruta inicialmente ensayada por nuestro grupo de investigación trató de aplicar el protocolo *one-pot* desde el yodoalquino **43c** para obtener directamente la sulfonil-ciclobutenona **46u-O₂** (Esquema XII.36).



Esquema XII.36

Desafortunadamente, el ácido 4-(metilsulfonil)fenil borónico no funciona en estas condiciones de reacción, originando una mezcla compleja. Diseñamos entonces una ruta alternativa utilizando en su lugar el ácido 4-(metiltio)fenil borónico pero conservando el protocolo *one-pot*. Afortunadamente, este ácido borónico respondió muy bien a las condiciones de reacción, obteniéndose la ciclobutenona **46u** con un 71% de rendimiento. La oxidación del grupo metilsulfuro utilizando ácido metacloroperbenzoico originó la sulfonil-ciclobutenona **46u-O₂**, molécula que ya presenta capacidad inhibitoria de la COX-II. La transformación del grupo carbonilo al metileno por reacción de Wittig permitió acceder finalmente a la molécula **63**, con una actividad inhibitoria y una selectividad COX-I/COX-II mucho mayores.

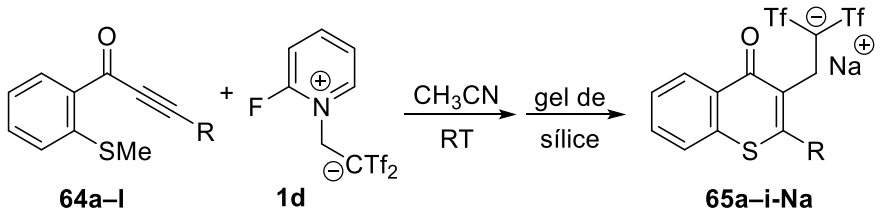
Si comparamos ambas rutas sintéticas podemos observar que la original alcanza el producto final en cinco etapas con un rendimiento global del 1.7%. Por el contrario, nuestra ruta consigue reducir el número de etapas a cuatro con un rendimiento global del 27%. Además de la mejora significativa del rendimiento global, conseguimos evitar etapas experimentalmente engorrosas en las que se usan amalgamas y reducciones con zinc que presentan rendimientos bajos en la síntesis original.

XII.1.5. Capítulo 5: Reactividad divergente en inonas: ciclación por 3,4-difuncionalización *versus* bis-ciclación

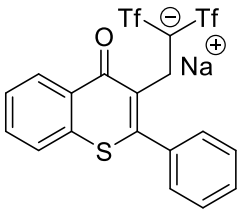
La siguiente familia de alquinos que nos planteamos estudiar fueron las inonas conjugadas. Nuestro estudio comenzó con el tratamiento de la inona **64a** en las condiciones optimizadas, es decir, en acetonitrilo como disolvente a temperatura ambiente y utilizando la sal de 2-fluoropiridinio **1d** como generador *in situ* de $Tf_2C{=}CH_2$. Sorprendentemente, en vez de obtenerse el ciclobuteno esperado, aislamos en su lugar la bis(triflil)tioflavona **65a** (Esquema XII.37). Esta reacción implica una serie de características positivas. En primer lugar, se forma un nuevo enlace C−S, que origina un núcleo heterocíclico denominado tioflavona, presente en una gran cantidad de productos naturales. Además, en el mismo paso, se incorporan dos grupos fluorados a la estructura, todo ello en unas condiciones de reacción suaves, sin el uso de metales u otro tipo de catalizador.

Con este primer ensayo tan positivo decidimos explorar el alcance de la reacción con las inonas **64b-l** (Esquema XII.37). Observamos que los grupos metoxilo, metilo y bromo en el sustituyente arilo del triple enlace son bien tolerados, obteniéndose las tioflavonas **65b-d** con rendimientos comprendidos entre 39 y 77%. Cuando este resto arilo simple es reemplazado en el alquino por otro tipo de arilo, como los derivados de naftaleno, o heterociclos como el indol, el tiofeno o el ferroceno en las inonas **64e-i**, también se obtienen las correspondientes tioflavonas **65e-i**. Sin embargo, cuando empleamos sustituyentes desactivantes en las inonas de partida **64j** y **64k**, así como una cadena alifática de *n*-butilo **64l**, la reacción no origina las correspondientes tioflavonas **65j-l**; recuperándose intactos los materiales de partida.

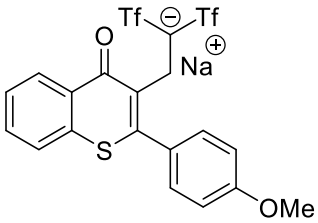
Como ocurría con algunos productos de Capítulos anteriores, estas moléculas son portadoras del grupo extremadamente ácido $CHTf_2$. Esto provoca la disociación rápida y completa del protón, que se intercambia por un catión sodio al ser sometidos los productos **65a-i-Na** a purificación por cromatografía en columna sobre gel de sílice. Por ello, no es posible detectar el protón ácido por ^{1}H-RMN, pero si es posible detectar el catión Na^+ por medio de ^{23}Na-RMN y por SEM-EDX.



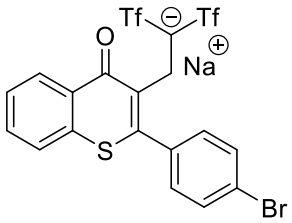
64a–l **1d** **65a–i-Na**



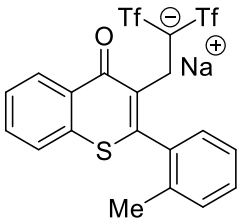
65a-Na (41%, 5 h)



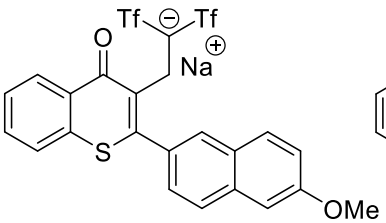
65b-Na (70%, 1 h)



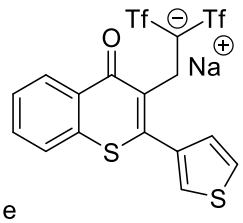
65c-Na (39%, 7 h)



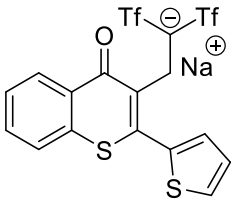
65d-Na (74%, 2 h)



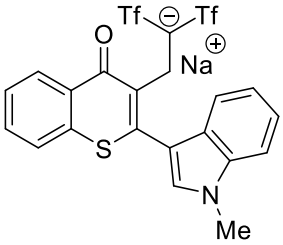
65e-Na (77%, 3 h)



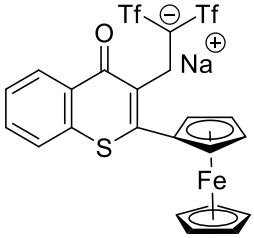
65f-Na (67%, 2 h)



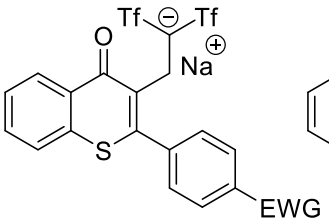
65g-Na (57%, 1 h)



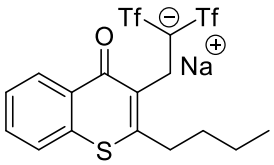
65h-Na (64%, 2 h)



65i-Na (39%, 1 h)



65j-Na (EWG = NO_2, 0%, 24 h)
65k-Na (EWG = CF_3, 0%, 24 h)

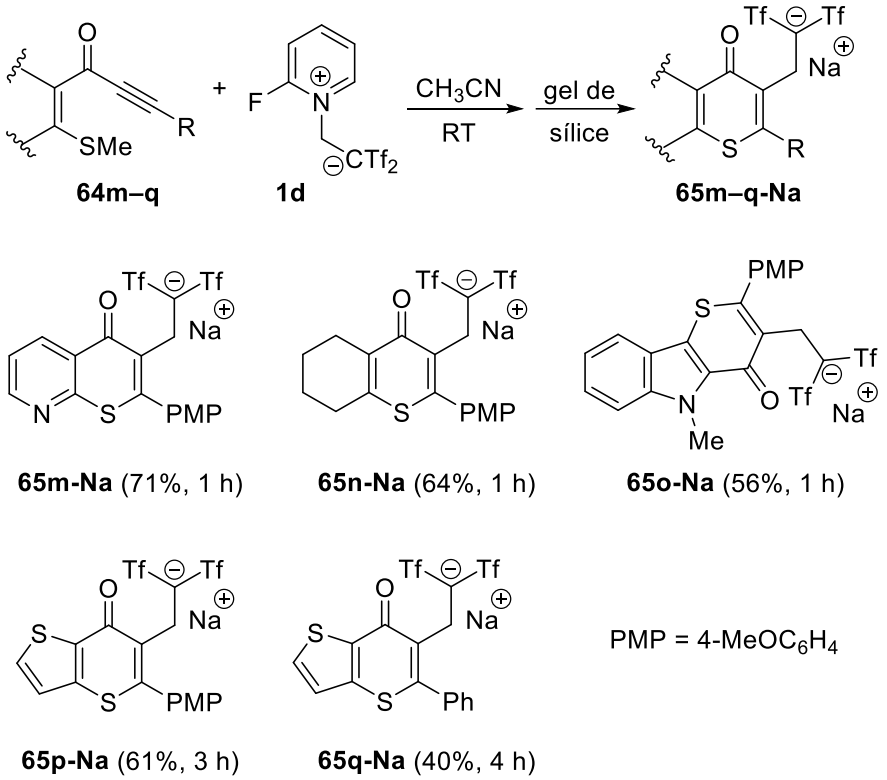


65l-Na (0%, 24 h)

Esquema XII.37

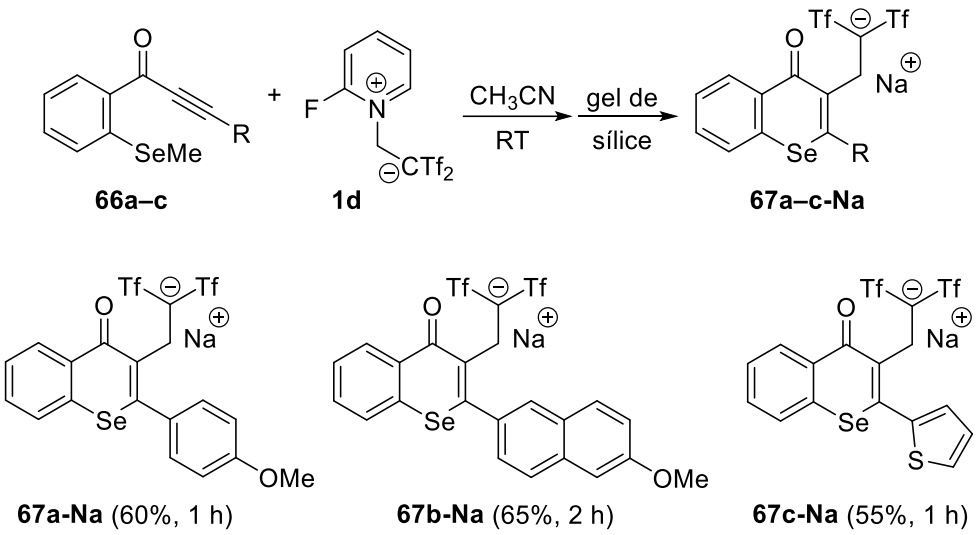
El alcance de la reacción también se exploró realizando cambios estructurales en el sustituyente MeS-arilo de las inonas de partida. El cambio del anillo de benceno

por otros ciclos como piridina, ciclohexeno, indol y tiofeno dio como resultado las moléculas esperadas **65m-q** (Esquema XII.38).



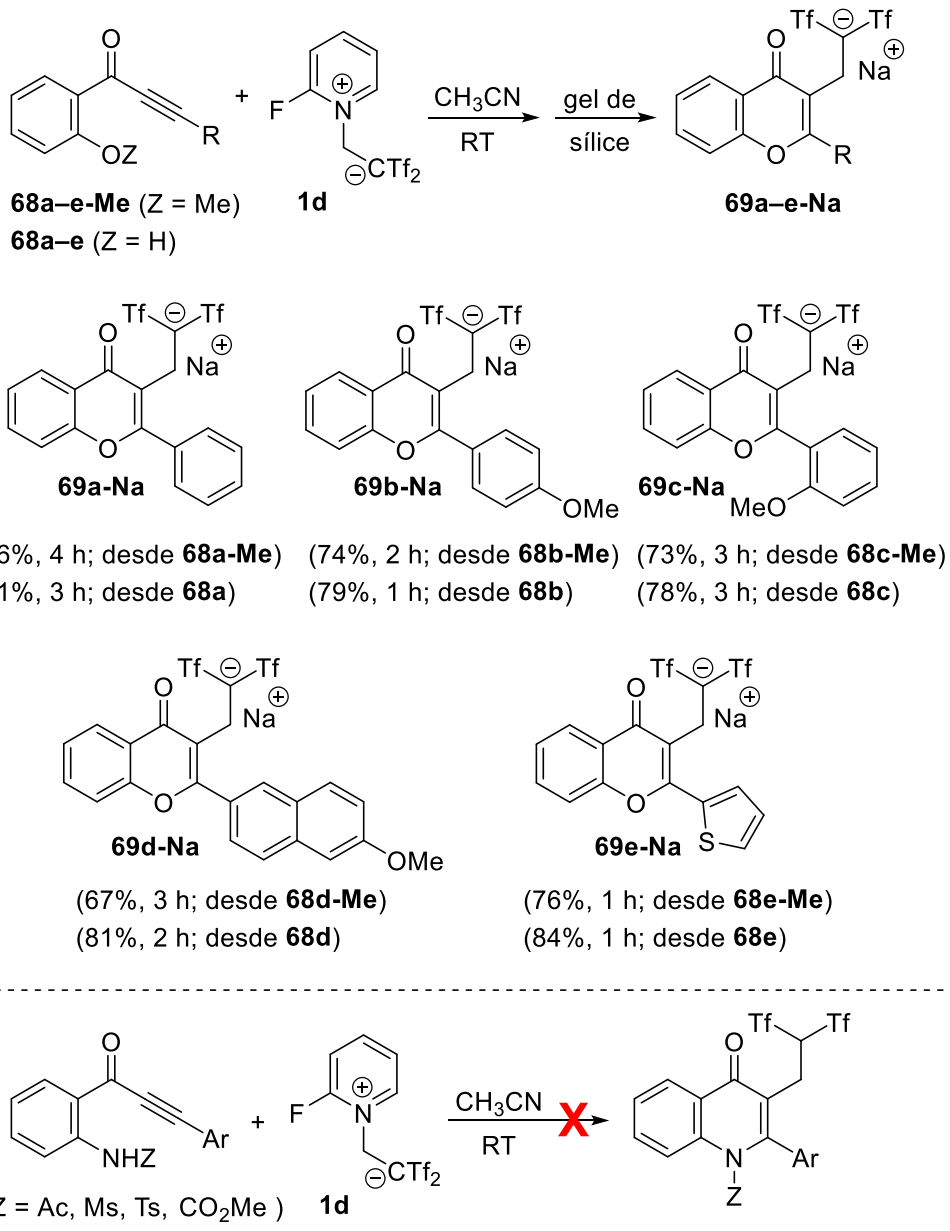
Esquema XII.38

Teniendo en cuenta la importancia química y biológica de los compuestos de selenio nos propusimos extender la metodología a inonas portadoras de este elemento. También, desde un punto de vista de la reactividad, resulta interesante conocer cómo afecta el cambio del nucleófilo de la reacción cuando pasamos del grupo -SMe a -SeMe. Afortunadamente, cuando hicimos reaccionar las (metilseleno)inonas **66a-c** con el zwitterión **1d** se formaron las selenoflavonas **67a-c** como únicos productos (Esquema XII.39).



Esquema XII.39

La naturaleza del nucleófilo también se puede modificar para incorporar una agrupación oxigenada. Esta puede introducirse de manera análoga a las anteriores, a través de metoxi-inonas **68a-e-Me** o bien mediante las hidroxi-inonas **68a-e**. Partiendo de estas oxi-alquinonas y aplicando las mismas condiciones de reacción, obtenemos las bis(triflil)flavonas **79a-e** con rendimientos comprendidos entre 56 y 84% (Esquema XII.40).



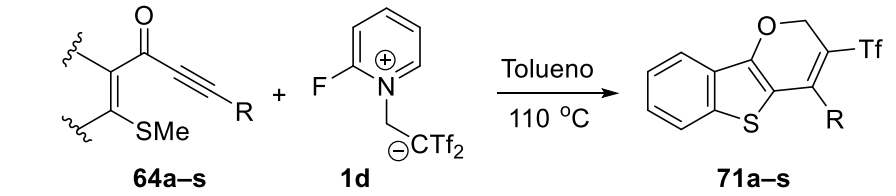
Esquema XII.40

Desgraciadamente, cuando intentamos extender la metodología a los análogos nitrogenados **70**, estos permanecieron inertes en las condiciones de reacción ensayadas (Esquema XII.40).

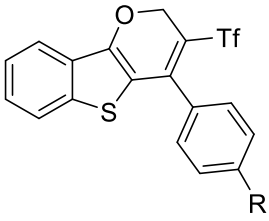
Una vez estudiadas en profundidad las posibilidades que ofrecen las inonas en este proceso de ciclación-funcionalización secuencial, ensayamos otras condiciones de reacción con el fin de conseguir productos alternativos.

El primer cambio introducido en el procedimiento fue un incremento en la temperatura al tratar la MeS-inona **64a** con el zwitterión **1d** en acetonitrilo, a 80ºC.

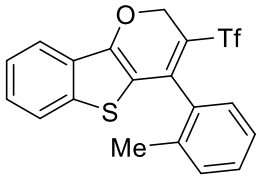
Estas condiciones provocan la formación de un nuevo tipo de compuesto, el 2*H*-pirano fusionado **71a** (Esquema XII.41).



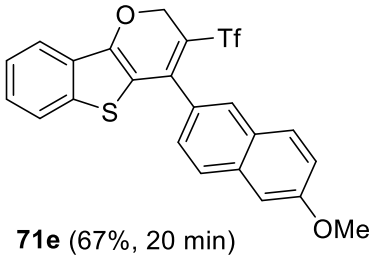
64a–s **1d** **71a–s**



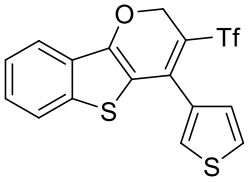
71a (R = H, 53%, 15 min)
71b (R = OMe, 82%, 10 min)
71c (R = Br, 56%, 15 min)



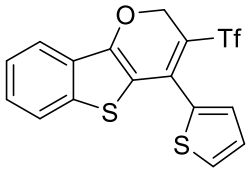
71d (75%, 15 min)



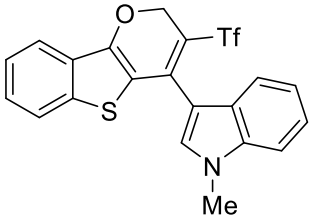
71e (67%, 20 min)



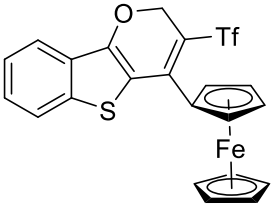
71f (64%, 20 min)



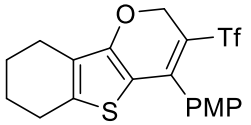
71g (71%, 10 min)



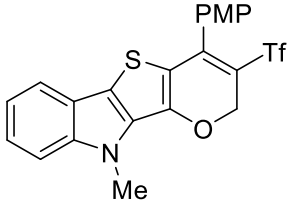
71h (76%, 15 min)



71i (22%, 10 min)[a]

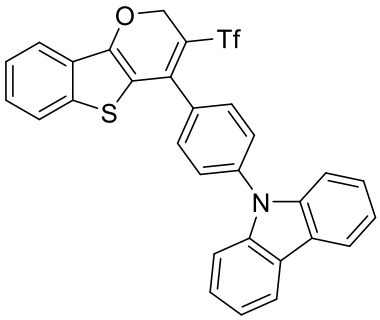


71n (71%, 15 min)

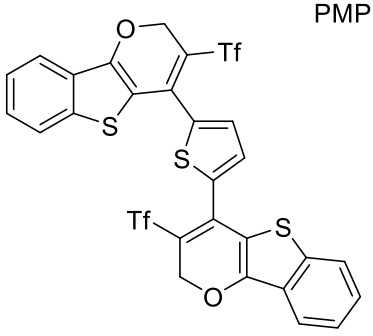


71o (55%, 15 min)

PMP = 4-MeOC$_6$H$_4$



71r (65%, 10 min)



71s (77%, 15 min)

[a] Descomposición parcial durante la purificación por cromatografía en columna.

Esquema XII.41

El problema principal era que se obtenía como producto minoritario, ya que se forma una mezcla de la tioflavona **65a** y 2*H*-pirano **71a** en proporción 2:1. Aun siendo productos fáciles de separar cromatográficamente, el procedimiento carece de utilidad sintética por la baja selectividad. No obstante, la formación de estructuras tipo **71a** resulta de gran interés, lo que nos llevó a investigar su síntesis selectiva optimizando las condiciones de reacción.

De este primer ensayo se deduce que la temperatura es un factor fundamental en la formación de la estructura **71a**. El acetonitrilo posee un punto de ebullición de 82ºC, por lo que si queríamos aumentar la temperatura era necesario un cambio de disolvente. En este caso, no es posible utilizar un tubo cerrado para aumentar la temperatura de la reacción por encima del punto de ebullición del disolvente, ya que es necesario añadir el zwitterión **1d** a la disolución caliente de inona. Este punto es clave, ya que se favorece la formación del triciclo **71a** en el mismo momento que el zwitterión **1d** entra en contacto con el medio de reacción caliente. Si se sigue el procedimiento habitual de reunir los reactivos y disolvente a temperatura ambiente y a continuación calentar progresivamente la reacción, se está favoreciendo la formación de la tioflavona **65a**, pues esta empieza a formarse a temperatura ambiente. El producto **71a**, solo es capaz de formarse a alta temperatura, por tanto, para cuando el medio de reacción ha alcanzado la temperatura adecuada gran parte de la inona ya se ha consumido para formar la tioflavona **65a**, originándose una mezcla con el 2*H*-pirano **71a** como producto minoritario.

Afortunadamente, aunque el zwitterión **1d** es insoluble en disolventes apolares a temperatura ambiente, no lo es a alta temperatura. El tolueno resultó ser el disolvente ideal por su mayor punto de ebullición (110ºC). Al tratar una disolución de la inona **64a** en tolueno, previamente calentada a 110ºC, con el zwitterión **1d**, obtuvimos el producto **71a** exclusivamente, sin observarse la formación significativa de la tioflavona **65a**. Por tanto, un simple cambio de temperatura, disolvente y momento de adición del zwitterión **1d**, nos permite modular la reactividad de las inonas frente a $Tf_2C{=}CH_2$, lográndose el acceso a dos estructuras fluoradas heterocíclicas totalmente diferentes entre sí.

Este nuevo proceso domino permite el acceso directo, sin el uso de metales, a una estructura tricíclica fusionada con la formación simultanea de enlaces C−S, C−O y C−C. Con las condiciones optimizadas, obtuvimos una serie de compuestos

71 con diferentes sustituyentes (Esquema XII.41). Los triciclos **71a-s** se obtienen con rendimientos de moderados a buenos, excepto el ejemplo **71i** con solo un 22% debido a diversas reacciones secundarias. La metodología también puede aplicarse a sustratos dobles como **64s**, obteniéndose el bis-2*H*-pirano **71s** (Esquema XII.41).

La estructura de los triciclos **71** se confirmó totalmente a través del análisis por difracción de rayos X de monocristal del compuesto **71a** (Figura XII.7).

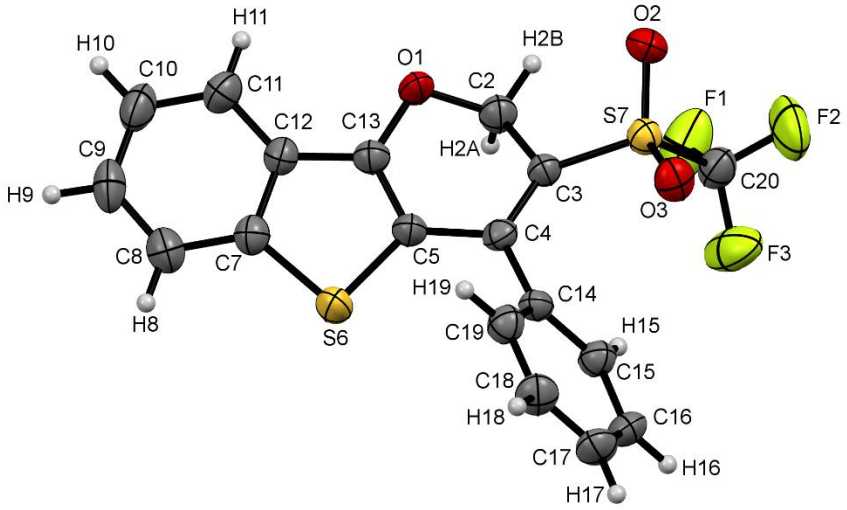
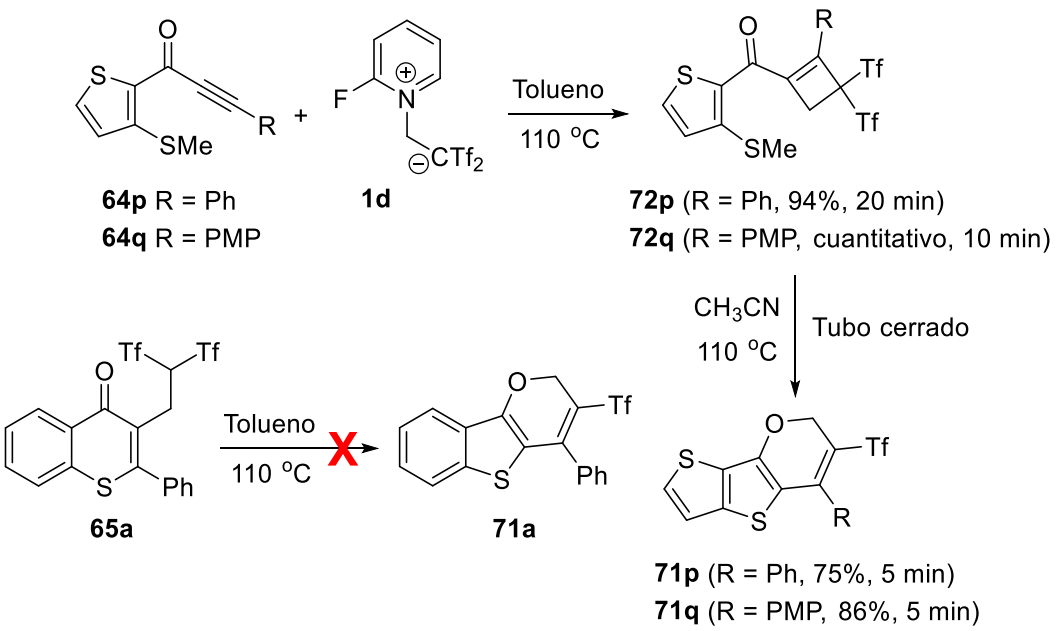


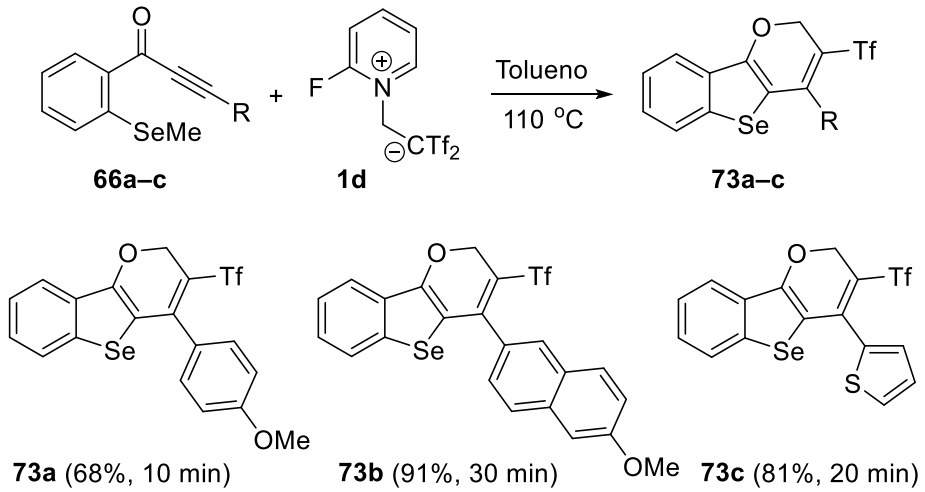
Figura XII.7

En un principio pensamos que los biciclos tipo **65** y los triciclos tipo **71** podrían estar relacionados, tratándose uno del producto de control cinético y el otro de control termodinámico, respectivamente. Para aclarar esta duda, calentamos el biciclo **65a** en tolueno a 110ºC, pero sin observarse evolución a ningún producto (Esquema XII.42). Algo desconcertante fue la obtención de los ciclobutenos **72p** y **72q**, con rendimientos muy altos, a partir de las MeS-inonas derivadas del tiofeno **64p** y **64q**. Afortunadamente, el tratamiento de estos ciclobutenos en acetonitrilo, a 110ºC en tubo cerrado condujo a los esperados, en un principio, triciclos **71p** y **71q** (Esquema XII.42). A partir de estos resultados, concluimos que los ciclobutenos **72** son intermedios de reacción en la formación de los triciclos **71**; que los biciclos **65** no lo son y que tampoco se trata de los productos de control cinético. Ambos procesos son totalmente independientes y diferentes mecanísticamente.



Esquema XII.42

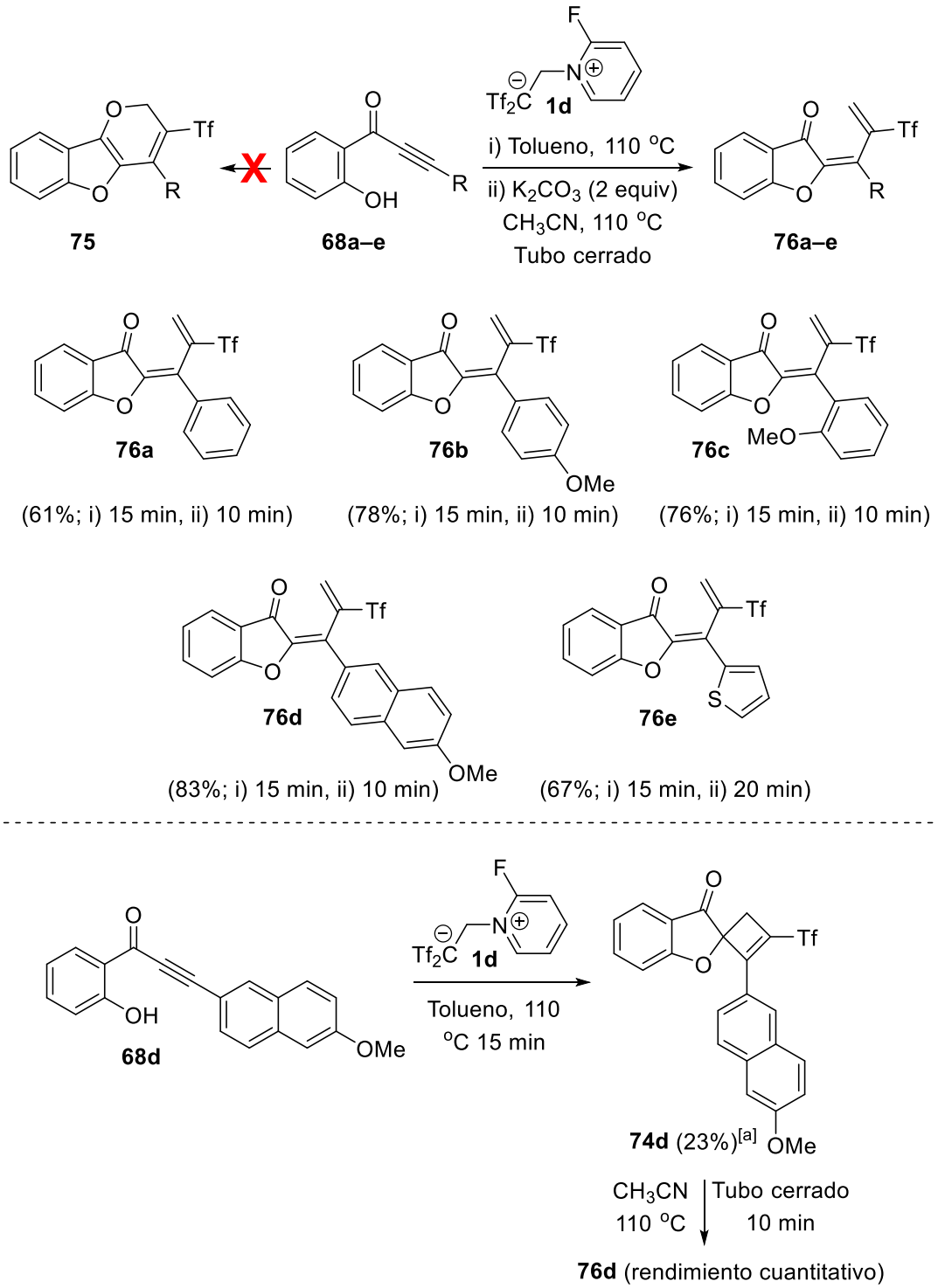
De manera análoga, estábamos interesados en aplicar las condiciones de reacción para la formación de triciclos tipo **71** a las inonas portadoras de selenio **66a-c**. Afortunadamente, estas se comportaron muy bien, originando los seleno-triciclos **73a-c** con buenos rendimientos (Esquema XII.43).



Esquema XII.43

Siguiendo con los cambios en el átomo del grupo nucleófilo, decidimos ensayar las inonas que contienen nucleófilo oxigenado, bien en forma de hidroxilo o de metoxilo. La reacción entre el zwitterión **1d** y los sustratos **68-Me** (sustituyente metoxilo) en tolueno a 110ºC origina mezclas complejas de reacción. Sin embargo,

al probar la reacción con las hidroxi-inonas **68** se obtiene una mezcla más sencilla de productos. Estos son de naturaleza inestable y solo en un caso fuimos capaces de aislar un posible intermedio, el ciclobuteno espirocíclico **74d** (Esquema XII.44).



[a] Descomposición parcial durante la purificación por cromatografía en columna.

Esquema XII.44

Para aumentar la nucleofilia del grupo hidroxilo y favorecer la reacción, se nos ocurrió tomar las mezclas obtenidas (crudo, sin purificación) y tratarlas con base. Tras probar diferentes bases, el carbonato potásico resulto ser la mejor opción, usando acetonitrilo como disolvente en tubo cerrado a 110ºC. En cortos tiempos de reacción, observamos como una mezcla de compuestos conducen a un solo producto por análisis CCF. Sorprendentemente, las inonas **68a-e** sufren un reagrupamiento que no origina los triciclos análogos esperados, sino los aductos **76a-e** (Esquema XII.44).

La estructura de dienona conjugada de cadena abierta que forman los aductos **76** fue completamente confirmada a través del análisis por difracción de rayos X de monocristal del compuesto **76e** (Figura XII.8).

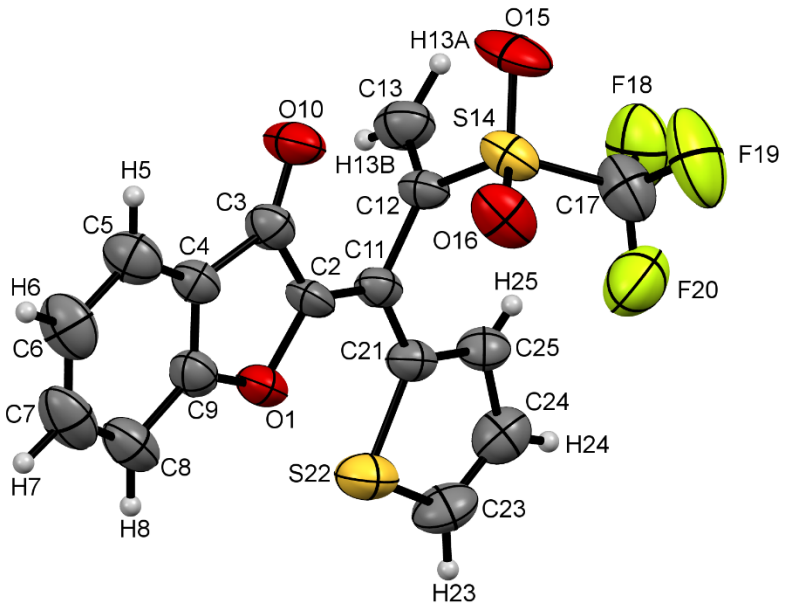


Figura XII.8

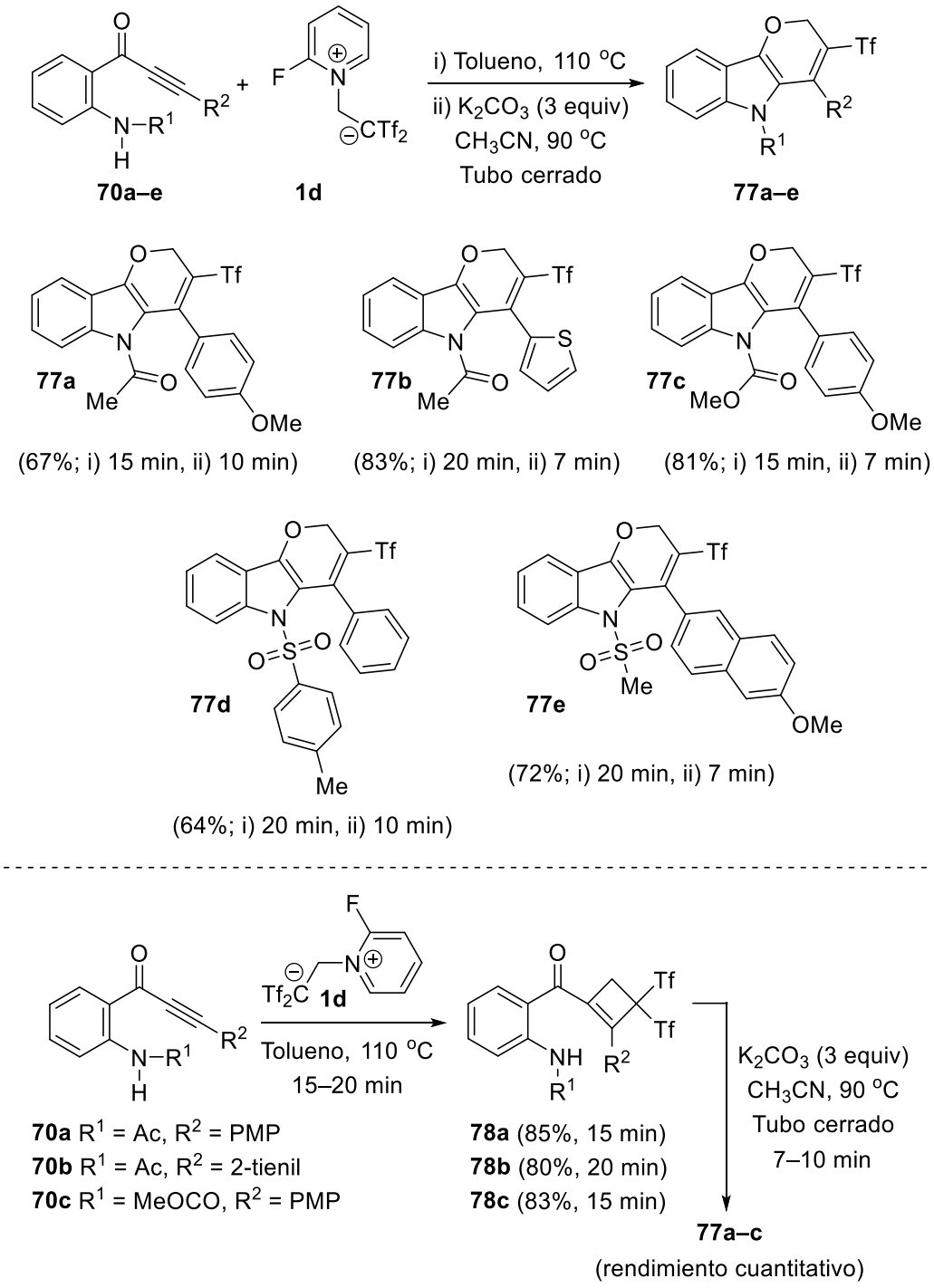
Una explicación tentativa a este resultado puede basarse en la longitud de enlace. Los enlaces C−S y C−Se son más largos que el enlace C−O, lo cual puede ser un factor crítico en la ciclación final.

Además, otro factor influyente puede ser la aromaticidad de los núcleos heterocíclicos de cinco eslabones que se forman en estos procesos. El orden de aromaticidad para estos anillos es furano<pirrol<tiofeno<selenofeno ya que el átomo de oxígeno es el más electronegativo de la serie y, por tanto, tiene menos tendencia a la cesión del par de electrones en la deslocalización aromática. En consecuencia, en el caso de los productos **76**, la formación de los furanos subsiguientes esperados

en un principio es la menos favorecida en términos electrónicos, respecto a los productos **71** (tiofenos), **73** (selenofenos) y **77** (pirroles), quedando en su forma de dienona conjugada. Estas dienonas conjugadas **76** son (triflil)vinil auronas y en consecuencia un tipo de flavonoide.

Cuando el intermedio de reacción espirocíclico propuesto **74d** se calentó en acetonitrilo a 110ºC en tubo cerrado se formó el compuesto **76d** (Esquema XII.44). Este hecho nos confirmó que las estructuras de ciclobuteno espirocíclico **74** son otro de los intermedios involucrados en la formación de los triciclos **71**.

Aunque en el caso de los biciclos **65** no fue posible expandir la metodología a inonas con nitrógeno como nucleófilo, creímos conveniente intentarlo en este caso, dado que son procesos completamente diferentes. Afortunadamente, aplicando unas condiciones similares a las desarrolladas para la obtención de las auronas **76**, fue posible aislar varios azatriciclos **77** con buenos rendimientos (Esquema XII.45).



Esquema XII.45

Parece, por tanto, que el aumento de la nucleofilia de los grupos OH y NHR por parte de la base es vital para que se complete el proceso. El grupo PMP en el producto **77a** puede remplazarse por naftilo, tienilo o fenilo sin que ello afecte significativamente a la eficiencia de la reacción. Tampoco parece afectar en exceso el cambio en el grupo protector del N. La estructura de indol-2*H*-pirano fusionado de

los compuestos **77** se confirmó por análisis de difracción de rayos X de monocristal del aducto **77b** (Figura XII.9).

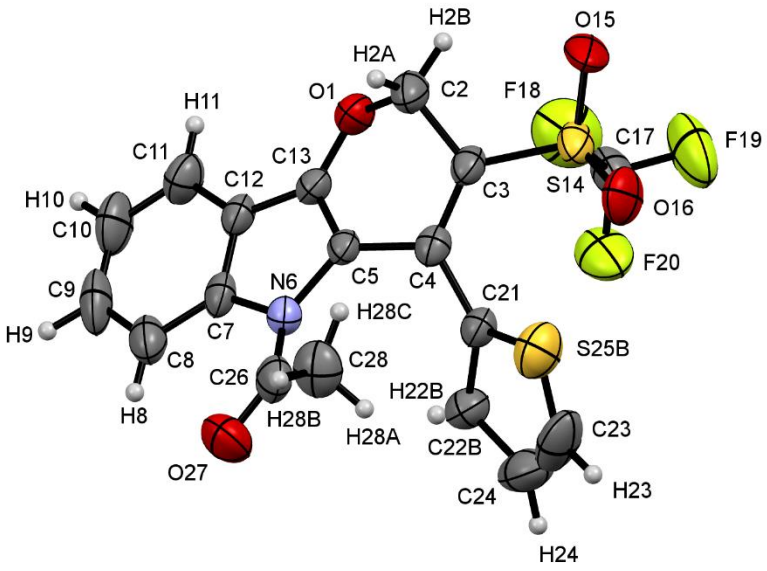
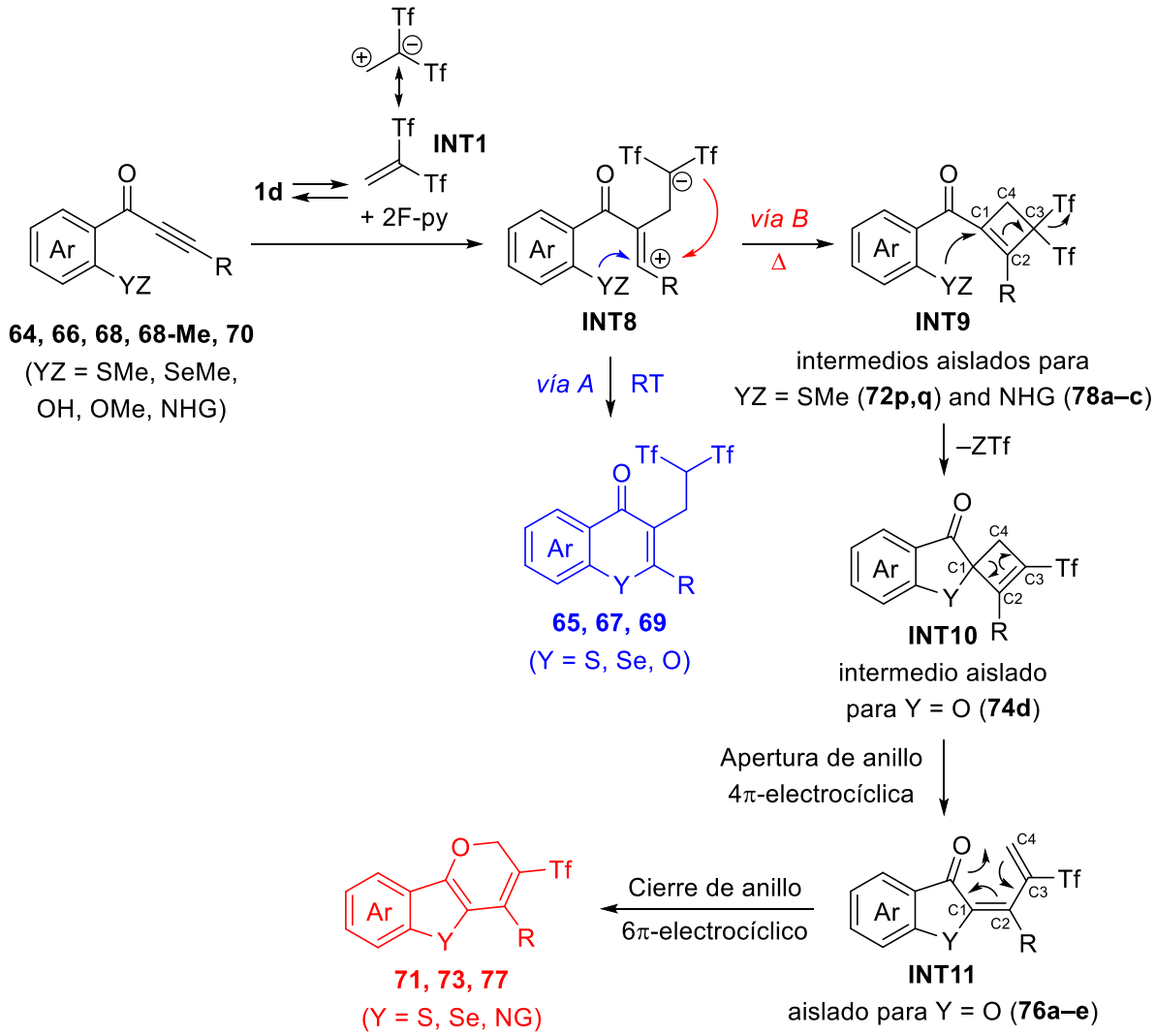


Figura XII.9

Para obtener evidencia de que los ciclobutenos tipo **72** también son intermedios en este proceso, llevamos a cabo la reacción entre las amido-inonas **70a-c** y el zwitterión **1d** a 110ºC, pero en ausencia del tratamiento con base (Esquema XII.45). Con estos experimentos fue posible aislar los ciclobutenos correspondientes **78a-c** con buenos rendimientos y comprobar que, si se someten estos a tratamiento térmico bajo condiciones básicas, se transforman en los triciclos **77a-c**.

A partir de los resultados obtenidos y los intermedios aislados propusimos un mecanismo de reacción para los dos procesos estudiados en este Capítulo (Esquema XII.46).



Esquema XII.46

Como se comentó en Capítulos anteriores, el primer paso es la formación en disolución de la molécula $Tf_2C{=}CH_2$ **INT1** a partir del zwitterión **1d**. La molécula **INT1** se encuentra en resonancia con su 1,2-dipolo correspondiente. A continuación, se forma un nuevo enlace C−C entre el carbono interno del alquino y el CH_2 de la molécula $Tf_2C{=}CH_2$, originándose la especie zwitteriónica **INT8**. Esta especie, en función del tipo de nucleófilo que ataque al carbocatión, podrá seguir la ruta de formación de uno u otro tipo de compuesto.

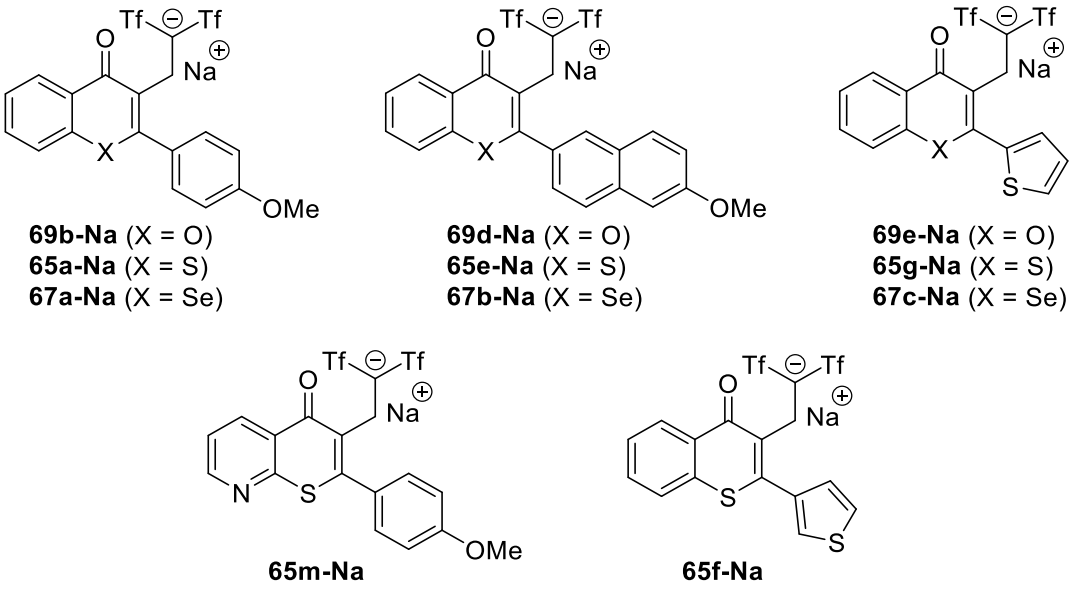
Si sufre el ataque por parte del nucleófilo YZ, se produce una heterociclación intramolecular que origina los biciclos **65**, **67** y **69** (*vía* A). Si por el contrario el ataque nucleófilo lo realiza el carbanión *gem*-bis-triflilo (CTf_2) se produce una carbociclación que genera los ciclobutenos **INT9** (*vía* B). La formación de los ciclobutenos **INT9** no

se produce a temperatura ambiente. Posteriormente se tiene que producir una adición nucleófila selectiva de los grupos funcionales -SMe, -SeMe, -OH o -NHP al carbono C1 de los ciclobutenos **INT9** para poder originar los ciclobutenos espirocíclicos **INT10**. A continuación, se produce un reagrupamiento mediante apertura 4π-electrocíclica, que conduce a las dienonas **INT11**, y cierre 6π-electrocíclico final que desemboca en los triciclos **71**, **73** y **77**. La secuencia de reacciones que conducen a estos productos finales debe estar motivada por el alivio de la tensión de anillo que supone pasar de los ciclobutenos **INT9** y **INT10** a la dienona intermedia **INT11**, así como por la aromatización parcial de las moléculas en sus núcleos de cinco eslabones.

Aunque la obtención y aislamiento de los ciclobutenos **72p** y **72q**, así como **78a-c**, el ciclobuteno espirocíclico **74d** y las dienonas **76a-e** fue casual, suponen una base empírica muy fuerte para respaldar el mecanismo de formación propuesto.

Dada la importancia biológica y el gran interés de los derivados de flavonas en el campo farmacológico, decidimos realizar una serie de ensayos de actividad biológica. Estos ensayos fueron realizados por el grupo del Prof. Dr. Claus Jacob, Universidad de Saarlandes (Saarbrücken, Sarre, Alemania), dado que carecíamos del conocimiento y equipamiento de laboratorio necesarios para llevarlos a cabo.

Se seleccionaron varias series de flavonas, tio- y selenoflavonas equivalentes entre sí, permitiendo comprobar cómo afecta el cambio de heteroátomo en la actividad dentro de cada serie. La comparativa entre diferentes series permite, a su vez, conocer cómo afecta el cambio de sustituyente en la actividad. También se realizaron ensayos sobre algunas flavonas independientes (Figura XII.10).



69b-Na (X = O)
65a-Na (X = S)
67a-Na (X = Se)

69d-Na (X = O)
65e-Na (X = S)
67b-Na (X = Se)

69e-Na (X = O)
65g-Na (X = S)
67c-Na (X = Se)

65m-Na

65f-Na

Figura XII.10

Se estudió la actividad frente a microorganismos unicelulares de diferente naturaleza, tales como bacterias (*Staphylococcus carnosus* y *Escherichia coli*), hongos (*Candida albicans*) y levaduras (*Saccharomyces cerevisiae*). Los datos de crecimiento de las diferentes cepas a las 4 y 24 horas en presencia de diferentes concentraciones de flavona, utilizando una disolución acuosa al 1% de DMSO como disolvente a temperatura ambiente, revelaron una actividad muy pobre frente a estos microorganismos.

La disminución del porcentaje de crecimiento a las 4 horas es pequeña y en algunos casos el porcentaje sube a las 24 horas. Esto demuestra que estos organismos son resistentes a la presencia de estos compuestos, siendo capaces de seguir reproduciéndose, manteniendo una población estable e incluso aumentándola a las 24h. Por tanto, la acción antimicrobiana de estas flavonas, independientemente de los patrones de sustitución estructural, es baja. Como ejemplo, en la Figura XII.11 se recogen las diferentes gráficas para la molécula **69b-Na**, mostrando el resto de moléculas ensayadas un comportamiento semejante.

Como nota aclaratoria, en las gráficas de la Figura XII.11 la actividad la marca la altura de las barras (menor altura = menor crecimiento = mayor actividad del compuesto). Los asteriscos mostrados en la parte superior de cada barra indican la significancia estadística del dato aportado. A mayor número de asteriscos (*, ** ó ***)

más fiable es, desde el punto de vista estadístico, el dato ya que los valores de desviación estándar (SD) obtenidos son menores.

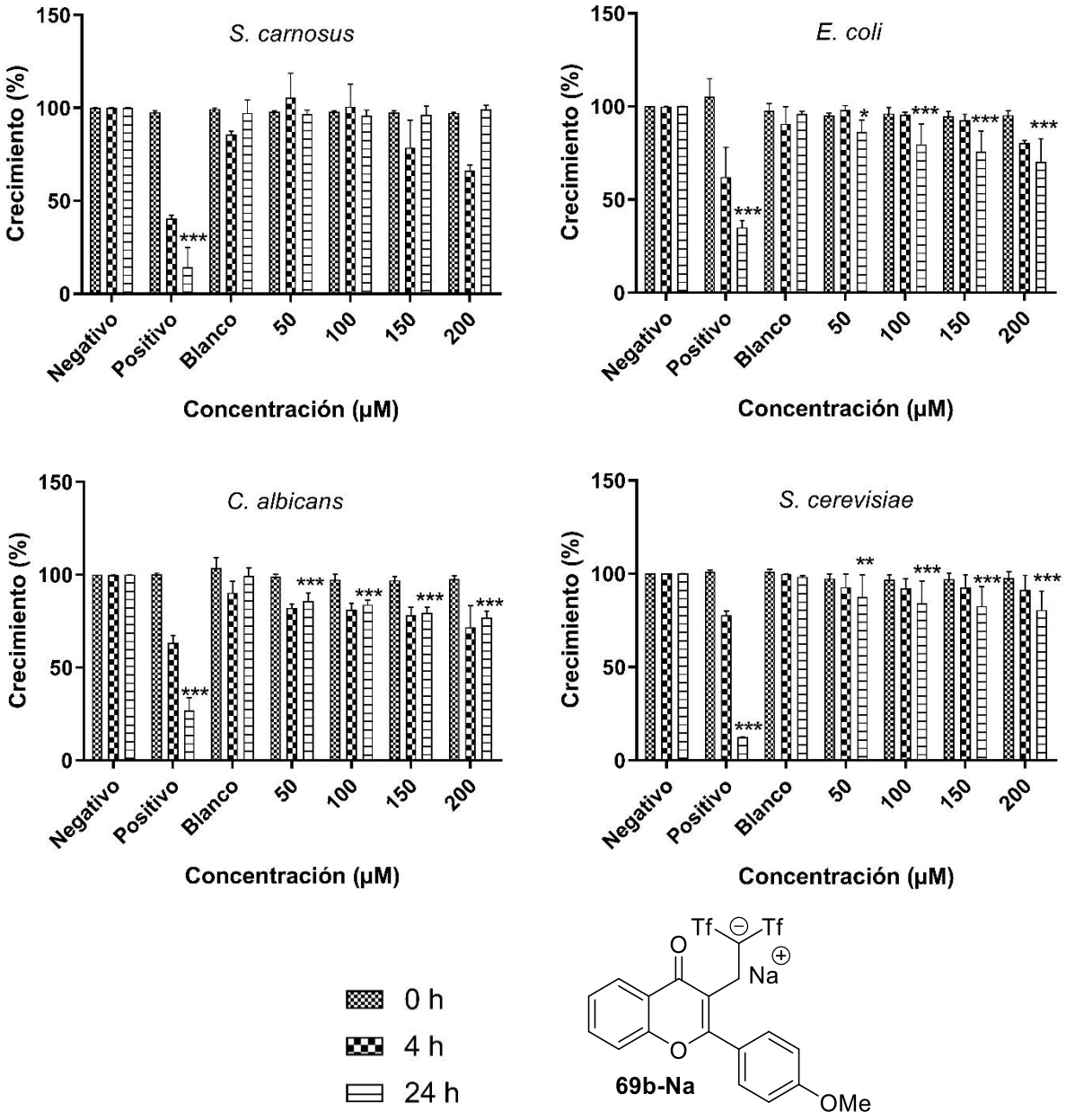


Figura XII.11

Afortunadamente, también se realizaron ensayos sobre un organismo pluricelular de la familia de los nematodos, *Steinernema feltiae*, gusanos entomopatógenicos microoscópicos (0.2 mm) (Figura XII.12).

Figura XII.12

El término entomopatógeno se refiere al microorganismo que es capaz de causar una enfermedad al insecto con el que interacciona, conduciéndolo a su muerte después de un corto período de incubación. Normalmente, la muerte no la produce el propio nematodo, sino las bacterias que viven en el interior de este, que al liberarse en el interior de la larva causan una infección mortal. Son utilizados en el control de plagas en cultivos, siendo capaces de parasitar larvas de diferentes moscas (*Lycoriella auripilla*, mosca del champiñón) y otras moscas del mantillo provocando su muerte antes de llegar a edad adulta.

Los ensayos de actividad frente a este nematodo se realizaron en las mismas condiciones que los anteriores y revelaron una respuesta positiva con una actividad significativa para determinadas flavonas. Al tratarse de un organismo pluricelular en un estado en el que no puede reproducirse, es decir, no pueden darse incrementos en la población, lo que se determina en este caso es la viabilidad frente a diferentes concentraciones de flavona a las 24 horas de iniciar la exposición. Los compuestos **69b-Na**, **65a-Na**, **67a-Na** y **67b-Na** son los que mayor nemotoxicidad presentan, reduciendo en algunos casos la viabilidad por debajo del 24% para la concentración más alta del compuesto (200 μM), lo cual indica que de la población total han muerto el 76% de los individuos. En la Figura XII.13 se muestra la gráfica para el compuesto **69b-Na** frente a este nematodo.

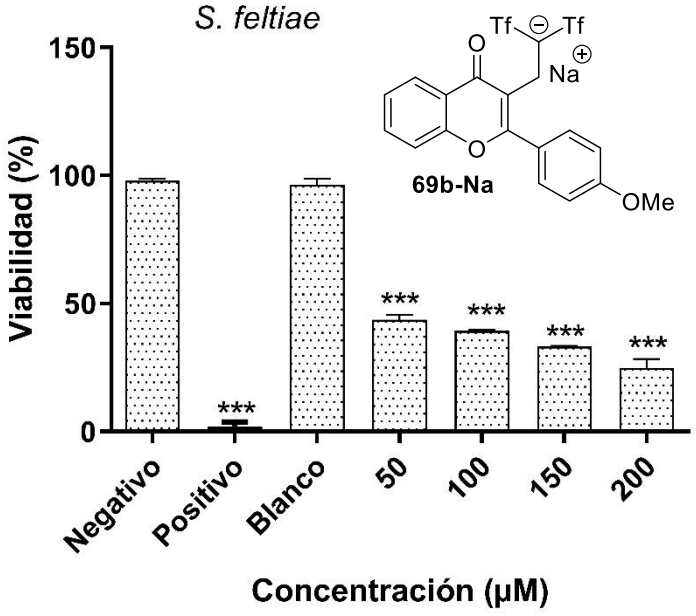


Figura XII.13

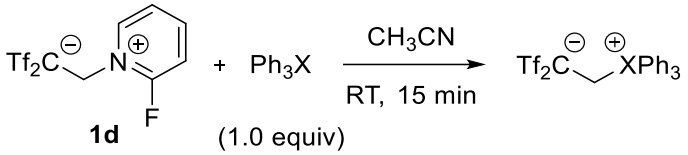
Dados los resultados, la serie de flavonas que poseen el sustituyente PMP en la posición dos del anillo es la más prometedora, observándose poca variación en los porcentajes de viabilidad al cambiar el heteroátomo de la posición uno.

XII.1.6. Capítulo 6: Síntesis y caracterización de fosfo-carbabetaínas estables

En este último Capítulo, dentro del apartado del estudio de la reactividad de zwitteriones tipo Koshar con alquinos, nos centraremos en la reactividad de diferentes tipos de fosfinas entre las que se encuentran las alquinilfosfinas, las cuales no se trataron en el Capítulo 2. Este estudio independiente se debe al comportamiento particular que presentan estos compuestos frente a la molécula $Tf_2C{=}CH_2$.

Los resultados expuestos a continuación están basados en un trabajo de colaboración con el grupo del profesor Hikaru Yanai. Nuestro grupo de investigación llevó a cabo el estudio de los aspectos sintéticos y la reactividad, mientras que Yanai y col. centraron su atención en las propiedades físico-químicas y estructurales de los compuestos obtenidos. Por ello, en este Capítulo discutiremos fundamentalmente el trabajo sintético. Aun así, se repasarán los resultados más relevantes extraídos de los cálculos computacionales y diferentes técnicas de caracterización.

Inicialmente y de manera casual, descubrimos que al enfrentar la molécula $Tf_2C{=}CH_2$ generada *in situ* con la trifenilfosfina **83a** se producía una reacción en la que los reactivos se consumían a gran velocidad (Esquema XII.47).



83a (X = P) — **81a** (99%, 98%[a])
84 (X = As) — **87** (90%)
85 ó **86** (X = Sb ó Bi) — no se observa reacción

[a] Reacción por el método retro-Michael con $Tf_2CHCH_2CHTf_2$.

Esquema XII.47

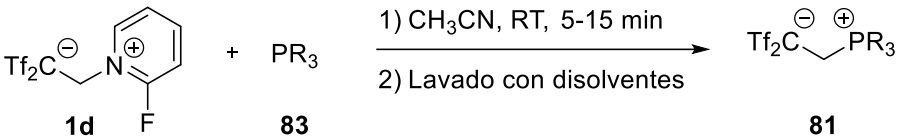
Intrigados por el producto formado, ajustamos los equivalentes empleados para evitar la presencia de reactivos sobrantes y facilitar su purificación, observando que la reacción se completaba perfectamente utilizando cantidades equimolares de zwitterión **1d** y trifenilfosfina **83a**. El compuesto sólido **81a** formado, tras su lavado con diclorometano, resultó ser el producto de *P*-alquilación de la trifenilfosfina. Esta especie zwitteriónica, denominada 1,3-fosfo-carbabetaína, se obtuvo con un

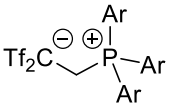
rendimiento casi cuantitativo en tan solo 15 minutos de reacción. Además, las condiciones de reacción ideales parecían ser las mismas utilizadas en Capítulos anteriores, esto es, acetonitrilo como disolvente a temperatura ambiente. El producto **81a**, es una sal estable al aire, a la luz y a la temperatura, pues no sufre alteración alguna si se calienta en tolueno a reflujo.

Decidimos explorar si esta fluoroalquilación era extensible al resto de átomos del grupo del fósforo (excepto el nitrógeno, ya estudiado por Yanai en un trabajo independiente anterior, como se mostró en los Antecedentes Generales). Usando el compuesto equivalente de la trifenilfosfina con arsénico en lugar de fósforo, la trifenilarsina **84**, descubrimos que también transcurría la reacción, obteniéndose el producto **87** con un 90% de rendimiento. Sin embargo, cuando ensayamos la reacción sobre los trifenilcompuestos de antimonio **85** y bismuto **86** no se observaron cambios en el material de partida.

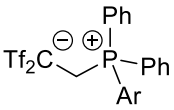
Aunque las condiciones utilizadas en el Esquema XII.47 parecían óptimas, decidimos ensayar los métodos alternativos para generar la molécula de $Tf_2C{=}CH_2$ también comentados en los Antecedentes Generales, por si aportaban alguna mejora adicional o una reactividad diferente. Utilizando el compuesto $Tf_2CHCH_2CHTf_2$ por el método retro-Michael se obtuvo el producto **81a** con un rendimiento de 98%. Al aplicar el segundo método, basado en la reacción de auto-condensación de bis(triflil)metano (Tf_2CH_2) con formaldehido, no observamos evolución hacia ningún producto, manteniéndose la trifenilfosfina **83a** inalterada. Aunque la reacción con $Tf_2CHCH_2CHTf_2$ daba buenos resultados, decidimos seguir usando el zwitterión **1d** dado que experimentalmente resulta más fácil de trabajar con él.

Una vez confirmado que las condiciones de reacción iniciales eran las mejores para estos procesos, decidimos explorar el alcance de la reacción sobre diferentes tipos de fosfinas. Primero se ensayaron fosfinas análogas sustituidas por diferentes anillos aromáticos **83b-i**, originando los productos **81b-i** (Esquema XII.48).

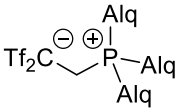




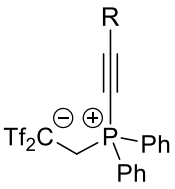
81b (Ar = 3,5-$Me_2C_6H_3$) 95%
81c (Ar = 4-$MeOC_6H_4$) 80%
81d (Ar = 2-MeC_6H_4) 97%
81e (Ar = 2,4-$Me_2C_6H_3$) 89%
81f (Ar = 2-$MeOC_6H_4$) 93%
81g (Ar = 2-furil) 95%



81h (Ar = 4-MeC_6H_4) 96%
81i (Ar = 2-MeC_6H_4) 93%



81j (Alq = *n*-Bu) 94%
81k (Alq = *t*-Bu) 96%



81l (R = Ph) 99%
81m (R = 4-$MeOC_6H_4$) 94%
81n (R = *n*-Bu) 99%
81o (R = Si^iPr_3) 97%

Esquema XII.48

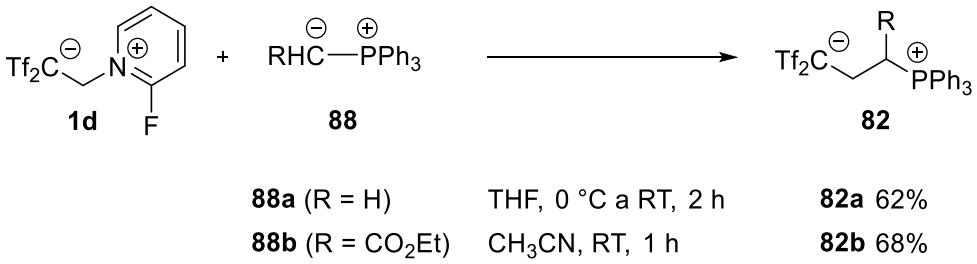
Estas fosfinas aromáticas incluyen arilos diferentemente sustituidos, incluyendo sustituyentes voluminosos para estudiar el efecto estérico en la reacción. Afortunadamente, los productos *P*-alquilados **81b-i** se obtuvieron con excelentes rendimientos, dejando patente una vez más que la molécula $Tf_2C{=}CH_2$ ignora los efectos estéricos y es condicionada por los electrónicos.

Al sustituir los grupos arilo de las fosfinas por restos alquilo, como son los *n*Bu y *t*Bu, se obtuvieron los productos esperados **81j** y **81k**, respectivamente sin observarse cambios significativos en la reactividad.

Finalmente, también estudiamos las alquinilfosfinas **83l-o**. Estas reaccionan de manera análoga al resto de fosfinas ensayadas, obteniéndose la *P*-alquilación en los productos **81l-o**, independientemente del sustituyente en el alquino. Especialmente interesante es el ejemplo **81m**. Con el fin de forzar la reacción de cicloadición [2+2] en el triple enlace, se colocó un arilo activado como es el 4-$MeOC_6H_4$. Sin embargo, la quimioselectividad del proceso es total, produciéndose exclusivamente la reacción sobre el átomo de fósforo, sin observarse trazas del ciclobuteno. También se probó a añadir un segundo equivalente de zwitterión **1d**, con el fin de hacer reaccionar al triple enlace una vez ya se ha alquilado el fósforo.

Sin embargo, ninguna reacción tiene lugar ya que la formación de la carbabetaína desactiva el alquino, haciéndolo inerte incluso forzando las condiciones de reacción y calentando a reflujo.

Una vez demostrada la posibilidad de utilizar las fosfinas como material de partida para obtener las 1,3-carbabetaínas **81a-o**, quisimos explorar la metodología en iluros de fósforo **88** para obtener 1,4-carbabetaínas. Inicialmente se ensayó un iluro no estabilizado **88a**, preparado a partir del tratamiento de bromuro de metiltrifenilfosfonio con *n*BuLi, obteniéndose la 1,4-carbabetaína **82a** por reacción con el zwitterión **1d** con un 62% de rendimiento. También, se probó un iluro de fósforo estabilizado **88b** que dio lugar al producto **82b** con un 68% de rendimiento (Esquema XII.49).



Esquema XII.49

Finalizado el trabajo sintético, se llevó a cabo el estudio estructural y de propiedades de enlace en las 1,3- y 1,4-carbabetaínas obtenidas, combinando las técnicas de resonancia magnética nuclear, difracción de rayos X de monocristal y cálculos computacionales.

Por resonancia magnética nuclear de fósforo, ^{31}P-RMN, se comparó el desplazamiento de la señal de este núcleo en la molécula **81j** y en la betaína **79b**, descrita en la literatura (Figura XII.14).

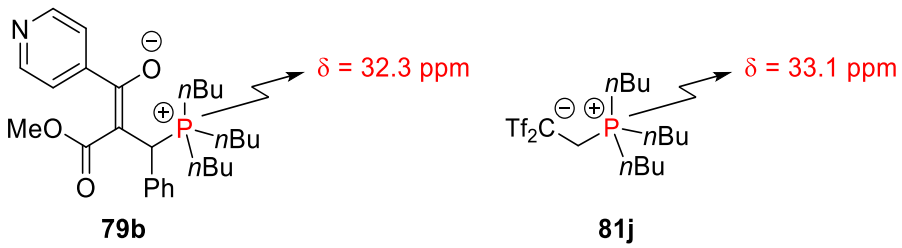
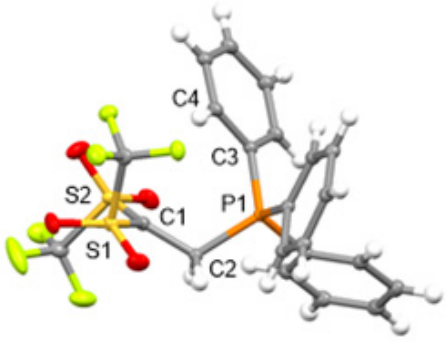


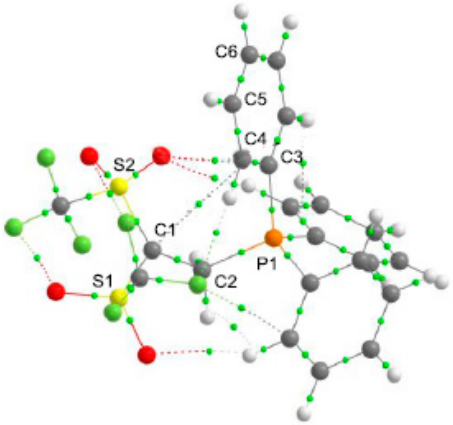
Figura XII.14

La diferencia de desplazamiento en ^{31}P-RMN entre ambas moléculas es muy pequeña. Además, el análisis de los espectros de ^{13}C-RMN de los productos **81** y **82** revela la presencia de carbonos aniónicos, con singletes que aparecen a δ = 55.5-60.5 ppm y δ = 62.9-63.1 ppm, respectivamente. Estos datos sugieren que, realmente, podemos considerarlas verdaderas carbabetaínas, con cargas bien localizadas dentro de las moléculas.

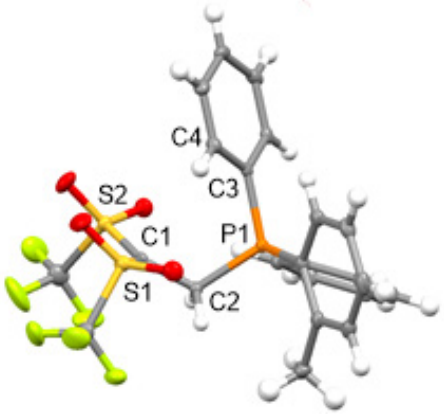
Se realizó el análisis cristalográfico de rayos X del producto **87**, de varias 1,3-carbabetaínas **81** y de las 1,4-carbabetaína **82a** y **82b**. En la Figura XII.15 (izquierda) se muestran los diagramas ORTEP de algunas estructuras seleccionadas.



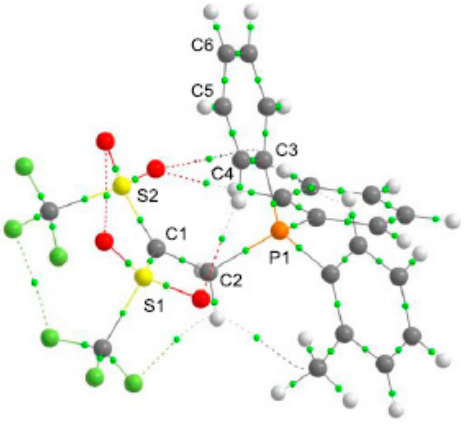
CF_3 (*anti*)



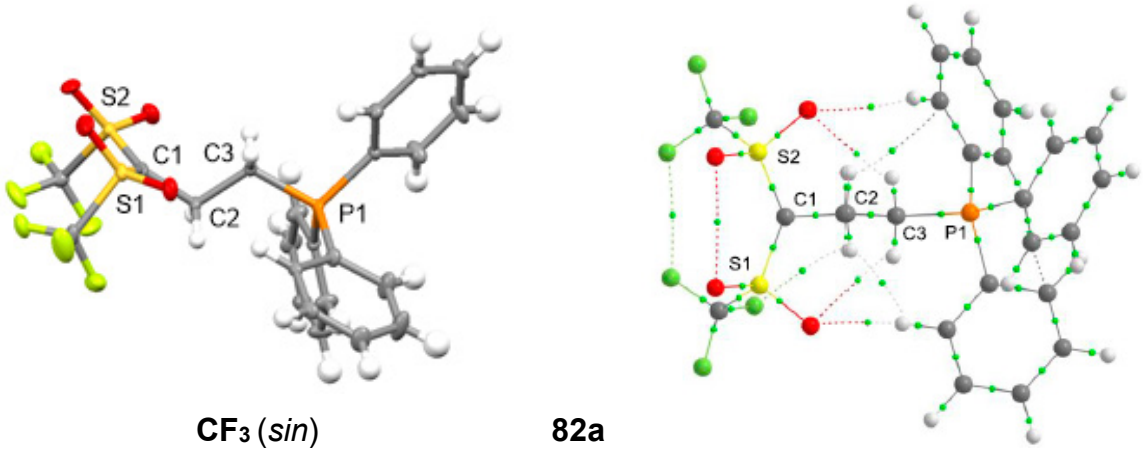
81a



CF_3 (*sin*)



81i



CF_3 (*sin*) **82a**

Estructuras cristalográficas | Proyecciones QTAIM

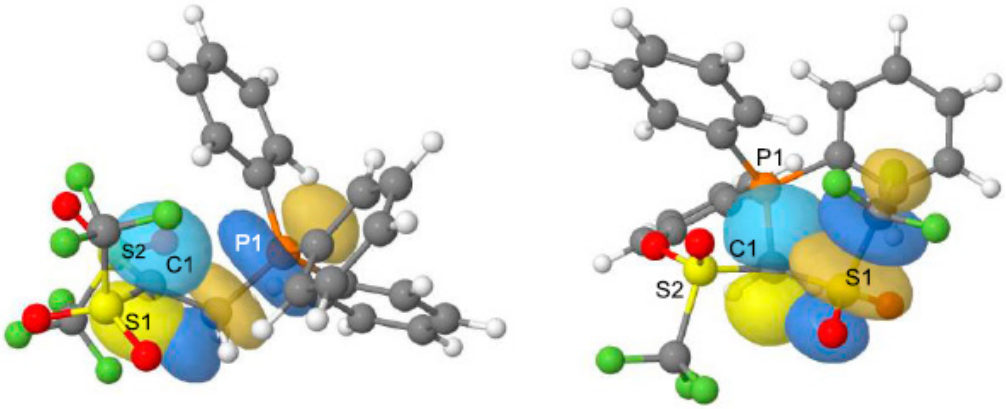
Figura XII.15

De los datos extraídos se observa que la geometría plana del carbono aniónico C1 y la estructura tetraédrica del fósforo catiónico P1 sugieren que no existen interacciones directas entre los átomos C1 y P1, o estas son muy débiles en el entorno cristalino. En particular, en las 1,4-carbabetaínas **82a** y **82b**, la orientación antiperiplanar alrededor del enlace C2−C3 hace que cualquier interacción intramolecular sea inviable. Otro aspecto estructural observado en los análisis por rayos X es la conformación que adoptan los grupos CF_3. Para algunos compuestos, como por ejemplo **81a**, adoptan conformación *anti* pero en otros se observa la configuración *sin*, como en los casos **81i** y **82a**.

La distancia de enlace entre C1 y los átomos de azufre S1/S2 a los que está unido es sensiblemente más corta que la distancia entre estos átomos de azufre y el carbono de los grupos CF_3, S−C(F_3). Como se comentó en los Antecedentes Generales, este fenómeno ya fue descrito por Yanai en un trabajo anterior cuando, precisamente, estudió la estructura de los zwitteriones de Koshar en detalle. El comportamiento conformacional de los dos grupos CF_3 y las distancias de enlace en el grupo $[Tf_2C]^-$, confirma la deslocalización del par de electrones libre del átomo C1 en un enlace sigma antienlazante $\sigma^*_{S-C(F3)}$, efecto conocido como hiperconjugación negativa.

Finalmente, se aplicaron cálculos DFT para optimizar las geometrias observadas del confórmero *anti* **81a** y el confórmero *sin* **81i**. Para ambos casos, los valores dados por los cálculos en cuanto a la carga de los átomos C1 y P1 son consistentes con el caracter aniónico y catiónico observado con las técnicas

anteriores. Sin entrar en detalles técnicos y valores numéricos, los cálculos NBO (*natural bond orbital*) sobre las propiedades orbitalarias revelaron que el orbital *p* (LP_{C1}) en el átomo C1 está parcialmente ocupado y la perturbación de este orbital con el adyacente $\sigma^*_{S-C(F3)}$ es bastante fuerte. Este resultado viene a apoyar la existencia del efecto de hiperconjugacion negativa comentado anteriormente. Tambien existe una interaccion, aunque mucho más débil entre LP_{C1} y el orbital σ antienlazante entre C2 y P1 (σ^*_{C2-P1}). Las proyecciones NBO para estas interacciones en **81a** se pueden observar en la Figura XII.16.



LP_{C1} / σ^*_{C2-P1} **LP_{C1} / σ^*_{S1-CF3}**

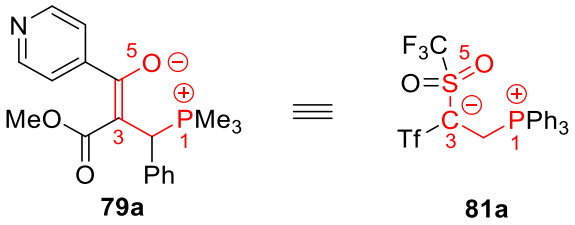
Figura XII.16

Los cálculos teóricos del orden de enlace entre C1−S y S−C(F_3) muestran que el primero es mayor que el segundo, aspecto que concuerda con las distancias de enlace experimentales obtenidas de los rayos X realizados.

Por tanto, los diferentes cálculos realizados permiten descartar cualquier tipo de interaccion orbitalaria directa entre C1 y P1, así como con los oxígenos de los grupos sulfona. Ello no quiere decir que no se den otras interacciones, aunque muy débiles entre el grupo R_3P^+ y el grupo $[Tf_2C]^-$. Curiosamente, se observa una leve interacción entre C1 y C4 (átomo de un grupo fenilo); concretamente el análisis NBO revela una interacción entre el orbital *p* de C1 y π-antienlazante del enlace C4−C5 (LP_{C1}/ π^*_{C4-C5}) en la molécula **81a**. Además, también se observaron algunas interacciones de enlace entre los átomos de oxígeno o flúor sulfónicos y los átomos de hidrógeno o carbono en los grupos arilo. La detección de estos enlaces débiles se obtiene a partir del análisis QTAIM (*quantum theory of atoms in molecules*), herramienta muy útil para analizar interacciones débiles. Las proyecciones

obtenidas por esta herramienta pueden observarse en la Figura XII.15 (derecha), en las cuales las esferas verdes son los puntos críticos de enlace (BCP), que representan gráficamente entre que átomos existe algun tipo de interacción.

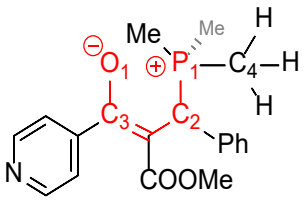
Cálculos semejantes sobre la molécula de referencia **79a**, descrita en la literatura y que presenta similitudes estructurales con **81a** (Figura XII.17), muestra un comportamiento muy diferente.



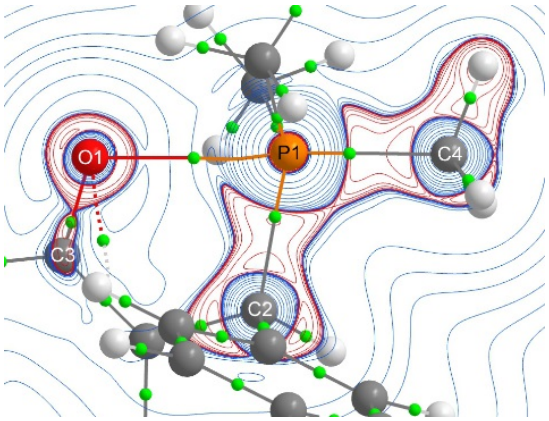
79a **81a**

Figura XII.17

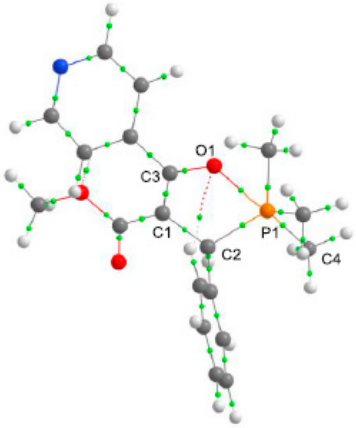
Como en el caso de **81a** y **81i**, haciendo uso de QTAIM observamos una interacción pronunciada entre las partes aniónica (O1) y catiónica (P1) de **79a** (Figura XII.18). En base a sus parámetros de enlace puede considerarse una interacción de trasferencia de carga (CT). Esta interacción no se observó en los equivalentes C1 y P1 de las moléculas **81**, ni tampoco entre los oxígenos de las sulfonas y P1. Una de las causas que facilitan la interaccion en **79a** es la geometria de bipirámide pseudotrigonal que adopta el átomo P1. En el análisis NBO (*natural bond orbital*) (Figura XII.18) puede observarse la interacción de transferencia de carga entre O1 y P1 a traves del solapamiento de los orbitales LP_{O1} y $\sigma^*_{P1–C4}$.



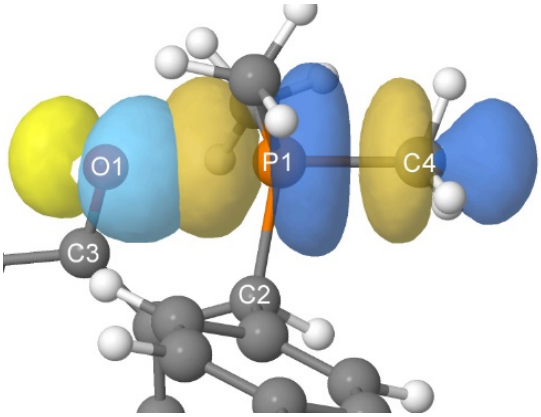
79a



Proyección QTAIM, centrado en el enlace O1···P1-C4



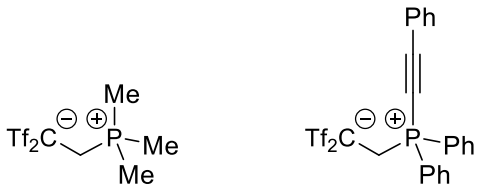
Proyección QTAIM, estructura completa



Proyección NBO, centrado en el enlace O1···P1-C4

Figura XII.18

Pensamos entonces, que la congestión estérica podría tener un papel importante para explicar las interacciones intramoleculares tan diferentes observadas en las estructuras de las moléculas **81** y **79a**. La aglomeración de grupos alrededor del átomo de fósforo podía ser una de las causas que impiden la interacción entre la parte aniónica y catiónica de estas moléculas. Por ello se analizaron computacionalmente las moléculas **81l** y **81a-Me**, más aliviadas estéricamente que las anteriormente estudiadas (Figura XII.19).



81a-Me **81l**

Figura XII.19

De nuevo, para ambos casos, no se detectan interacciones orbitalarias directas entre C1 y P1, ni entre C1 y los oxígenos de las sulfonas o los átomos de flúor. Aun así, eso no impide que se den interacciones atractivas débiles entre la parte aniónica y catiónica. Por tanto, si al disminuir la congestión estérica en el átomo de fósforo P1 no se facilita la interacción, la propia congestión alrededor del carbono aniónico C1 del grupo $[Tf_2C]^-$ puede ser la causante.

Por tanto, podemos concluir que los diferentes análisis realizados revelan una serie de interacciones débiles no covalentes entre el grupo R_3P^+ y los grupos $[Tf_2C]^-$, a veces denominadas "anión···π" y "anión···H−C", que sirven como factor de estabilización de las estructuras **81**. En el grupo $[Tf_2C]^-$, la hiperconjugación negativa, así como la congestión estérica alrededor del átomo de carbono aniónico, desempeñan un papel clave en la supresión de las interacciones directas por transferencia de carga con el átomo de fósforo catiónico.

XII.2. Reacciones de alquilación con zwitteriones de Koshar

En este apartado de la Memoria se ha llevado a cabo el estudio de reacciones de fluoroalquilación producidas por la molécula $Tf_2C=CH_2$ en una amplia variedad de heterociclos.

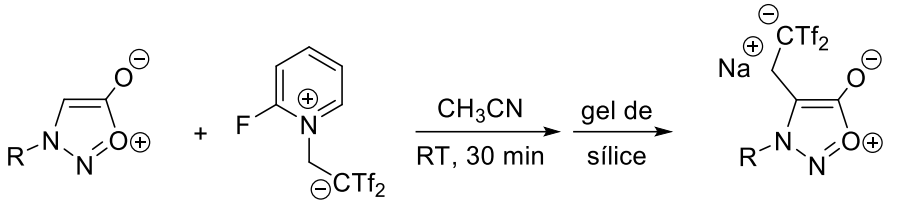
XII.2.1. Capítulo 7: Síntesis controlada y en ausencia de metales de bis-[(trifluorometil)sulfonil]etil heterociclos

En los Antecedentes Generales vimos que el grupo de Yanai demostró que era posible utilizar el zwitterión de Koshar de 2-fluoripiridinio **1d** como agente alquilante sobre fenoles. Estos anillos bencénicos son ricos en electrones, por tanto, muy proclives a sufrir sustituciones electrófilas aromáticas. Estos autores también han sido capaces de utilizar este zwitterión para alquilar compuestos organometálicos (magnesianos e hidruros de aluminio) y la posición α (ácida) de compuestos carbonílicos. Nuestro grupo de investigación observó que también es posible producir estas alquilaciones en estannanos, como se mostró en el Capítulo 2 de la presente Memoria.

Por tanto, queda patente, que la molécula $Tf_2C=CH_2$ es capaz de producir fluoroalquilaciones en anillos o posiciones ricas en electrones. Partiendo de la experiencia acumulada en trabajos anteriores, ambos grupos de investigación, estábamos interesados en saber si era posible extender o desarrollar esta metodología para la alquilación de heterociclos aromáticos ricos en electrones (π-excedentes) y otros heterociclos no aromáticos, pero con posiciones especialmente activadas. Fruto de esta colaboración se obtuvo la publicación que ha dado origen al presente Capítulo.

El grupo de heterociclos con el que iniciamos nuestra investigación fueron las sidnonas. Este heterociclo resulta especialmente interesante porque vaticinamos la posibilidad de que se produjeran dos reactividades muy diferentes entre sí. Por un lado, pensamos que el anillo de sidnona era capaz de dar la alquilación al ser un núcleo muy activado, pero también podía originar una cicloadición [3+2] con extrusión de CO_2 cuando se enfrenta a un dipolo, como puede ser el derivado de $Tf_2C=CH_2$. Con las dos posibilidades en mente tratamos las sidnonas de partida **89a-**

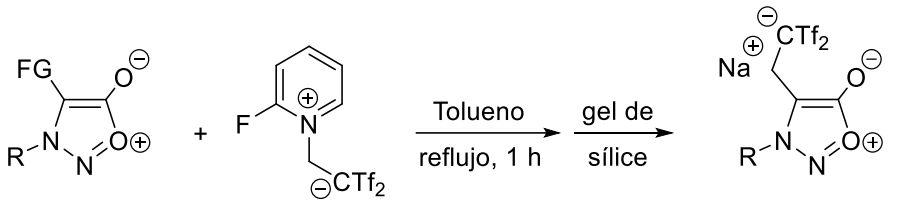
e con la sal de 2-fluoropiridinio **1d** en acetonitrilo a temperatura ambiente. En esta reacción, la posición C4 de las sidnonas **89**, fuertemente nucleófila, ataca a la posición electrófila de la molécula $Tf_2C=CH_2$ (Esquema XII.50).



89a R = Ph
89b R = 4-MeC_6H_4
89c R = 4-$MeOC_6H_4$
89d R = 4-$NO_2C_6H_4$
89e R = Me

1d

90a-Na (94%)
90b-Na (76%)
90c-Na (97%)
90d-Na (crudo)
90e-Na (97%)



89f R = Ph, FG = I
89g R = 4-MeC_6H_4, FG = I
89h R = 4-$MeOC_6H_4$, FG = I
89i R = Ph, FG = COMe
89j R = Ph, FG = 4-MeC_6H_4

1d

90a-Na (72%)
90b-Na (87%)
90c-Na (76%)
90a-Na (90%)

Esquema XII.50

Se generan así un nuevo de tipo de sidnonas **90a-e** alquiladas en C4 con excelente rendimiento. El ejemplo con 4-$NO_2C_6H_4$ **90d** no fue posible aislarlo puro debido a que descompone en cromatografía en columna sobre gel de sílice, pero su crudo puede utilizarse para reacciones posteriores.

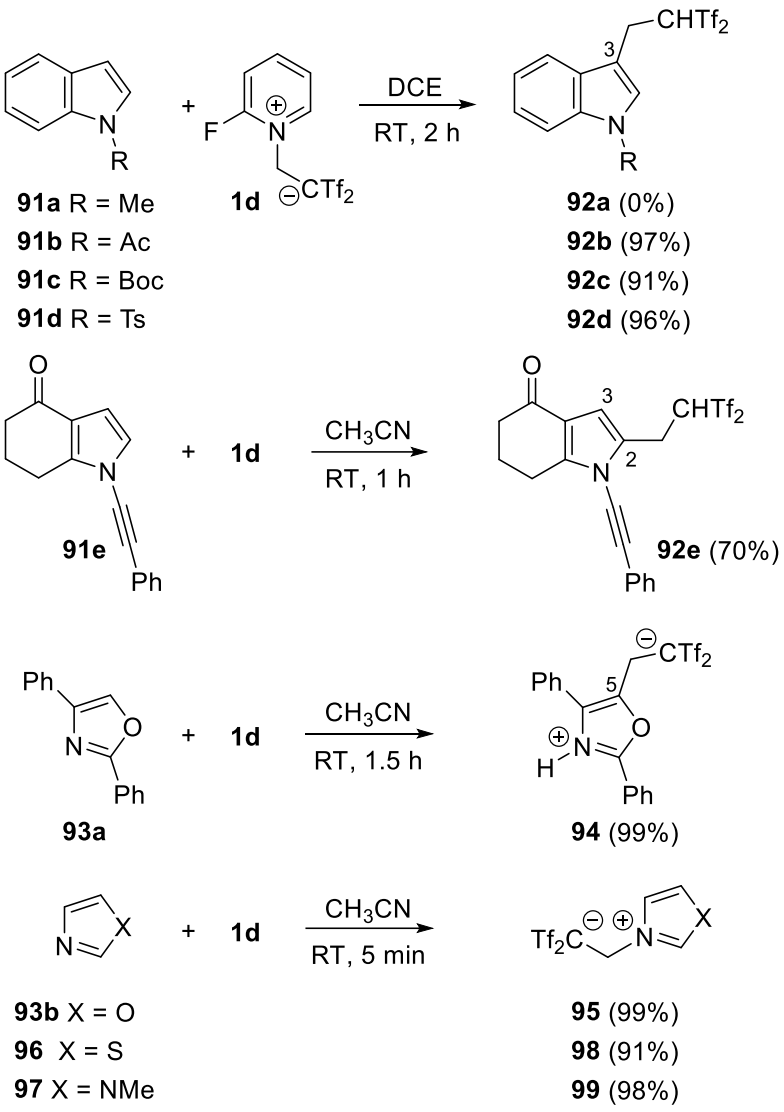
Con el fin de promover la otra reactividad prevista (cicloadición [3+2]), se probaron otras condiciones de reacción. Estas consistieron en el uso de ácidos de Lewis y calentamiento en tolueno a reflujo, pero en todos los casos se producía la descomposición de la sidnona de partida **89a-e** o de la sidnona alquilada **90a-e** cuando se intentaba la cicloadición con un segundo equivalente de zwitterión **1d**.

El último intento por conseguir la cicloadición [3+2] consistió en utilizar una serie de sidnonas de partida **89f-j** con la posición C4 sustituida por diferentes grupos. De esta manera la alquilación debería quedar bloqueada. Sorprendentemente, se

obtuvieron los aductos **90a-c**. Aun con la posición bloqueada, la naturaleza altamente nucleófila de esta posición hace que la molécula de $Tf_2C=CH_2$ sea capaz de sustituir los grupos presentes, dando lugar a una alquilación equivalente a la de las sidnonas **89a-e**, pero en condiciones de reacción más enérgicas (tolueno a reflujo). Solo la sidnona de partida **89j**, sustituida con un anillo de *para*-tolilo, quedó inalterada.

Como ocurría en Capítulos anteriores, el proceso de purificación en columna con gel de sílice ocasiona la desprotonación de la posición ácida del resto fluoroalquilado, sustituyendo el protón por un catión Na^+, obteniéndose las sales orgánicas **90a-e-Na**.

Con estas condiciones tan ventajosas, en las que no es necesario el uso de metales u otros catalizadores, así como la ausencia de irradiación para conseguir la bis(triflil)etilación de sidnonas, continuamos nuestro estudio para ver si eran aplicables a otros heterociclos activados. Ensayamos dichas condiciones en los derivados del indol **91a-d**, pirrol **91e** y oxazol **91a** (Esquema XII.51).

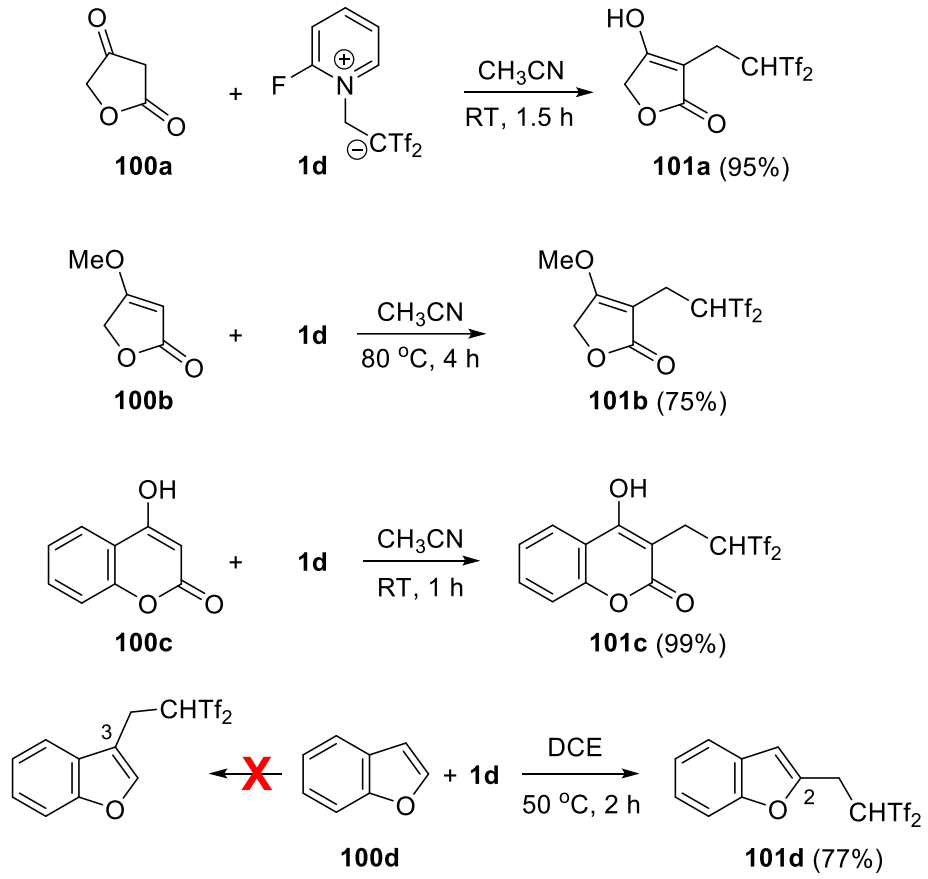


Esquema XII.51

Usando cantidades equimolares de zwitterión **1d** sobre los indoles **91a-d** observamos que para el ejemplo 1-metil-1*H*-indol **91a** se obtenía una mezcla compleja de reacción. Para controlar la alta reactividad de este núcleo se colocaron grupos electro-atractores en el nitrógeno. Con ello ya es posible obtener los indoles bis(triflil)etilados **92b-d** en la posición C3 de forma muy selectiva. También observamos que los indoles responden mejor en dicloroetano como disolvente, en lugar de acetonitrilo. El pirrol **91e** se preparó buscando demostrar la quimio- y regioselectividad del proceso. Se obtuvo exclusivamente el producto **92e**, sin producirse la posible cicloadición [2+2] sobre el alquino (inamina) ni la alquilación de la posición 3 del anillo pirrólico. Sobre el anillo de 2,4-difeniloxazol **93a** la alquilación que origina el producto **94** se produce en la posición C5. Sin embargo, en el oxazol

no sustituido **93b**, la reacción ocurre sobre el átomo de nitrógeno originando la sal **95**. Un comportamiento similar lo encontramos en los anillos análogos de tiazol **96** y *N*-metilimidazol **97**, que originan los productos **98** y **99** respectivamente. Las estructuras de los compuestos **92e** y **94** se confirmaron totalmente a través del análisis por difracción de rayos X de monocristal.

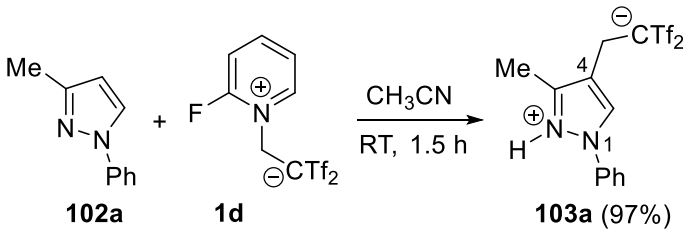
El siguiente grupo de heterociclos estudiados fue el de los oxaciclos, tanto aromáticos como no aromáticos (Esquema XII.52).



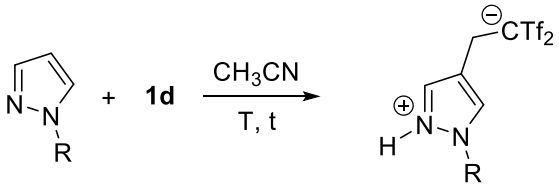
Esquema XII.52

El ácido tetrónico **100a**, el metil tetronato **100b**, la 4-hidroxi-cumarina **100c** y el benzofurano **100d** dan lugar a la *C*-bis(triflil)etilación de sus anillos, originando los productos **101a-d** con muy buenos rendimientos y con total selectividad. Se aplican condiciones de reacción muy similares en todos los casos excepto para **100b**, que es necesario calentar y para **100d**, que junto con un leve aumento de la temperatura, sustituimos el disolvente por dicloroetano. De nuevo, una caracterización estructural rigurosa nos llevó a confirmar completamente la estructura del ejemplo **101c** por difracción de rayos X de monocristal.

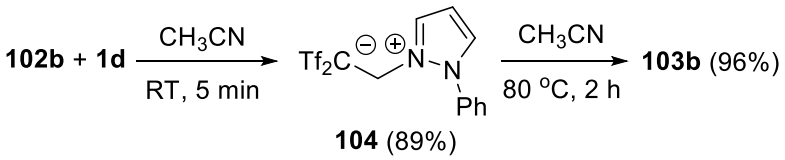
Seguimos explorando la aplicabilidad de la metodología sobre otros anillos nitrogenados, centrándonos ahora en el núcleo de pirazol. Como se muestra en el Esquema XII.53, la bis(triflil)etilación directa de este heterociclo se produce selectivamente en la posición C4, como ocurre en los ejemplos **102a** y **102b**, este último aplicando calor, conduciendo a los productos **103a** y **103b** respectivamente.



102a **1d** **103a** (97%)



102b R = Ph — **103b** (98%, 80 °C, 2 h)
102c R = Me — **103c** (98%, 90 °C, 5 h)
102d R = Bn — **103d** (97%, 90 °C, 3 h)
102e R = *i*-Pr — **103e** (98%, 90 °C, 2 h)

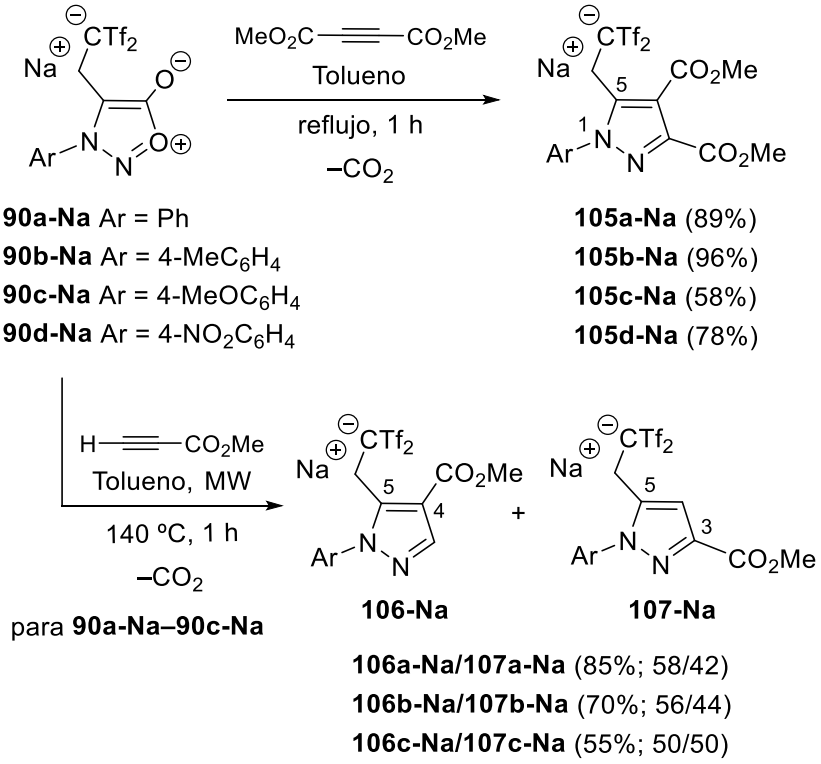


104 (89%)

Esquema XII.53

Cuando la reacción sobre **102b** transcurre a temperatura ambiente observamos la formación del producto *N*-alquilado **104**, que se puede convertir irreversiblemente en **103b** por calentamiento en acetonitrilo. Todos los aductos **103b-e** basados en pirazol se aislaron inicialmente como zwitteriones *N*-protonados, pero fueron convertidos fácilmente en sus correspondientes sales de sodio por tratamiento con NaOMe. Las estructuras de los aductos **103a** y **104** también fueron confirmadas por difracción de rayos X de monocristal. La selectividad encontrada hacia la posición C4 es consistente con la regioselectividad observada en las sustituciones electrófilas propias de los anillos de 1*H*-pirazol sustituidos en la posición 1.

Acabado el estudio sobre el alcance de la reacción, nos dimos cuenta que no existen en la literatura pirazoles con grupos triflilo en la posición C5. Pensamos entonces que podríamos aprovechar las sidnonas preparadas anteriormente para acceder a estas estructuras, mediante cicloadición [3+2] con alquinos y con extrusión de CO_2. De este modo, se tomaron las sidnonas 5-bis(triflil)etiladas **90a-d** (en forma de sales sódicas) y se trataron en presencia del alquino acetilendicarboxilato de metilo en tolueno a reflujo (Esquema XII.54).



90a-Na Ar = Ph
90b-Na Ar = 4-MeC_6H_4
90c-Na Ar = 4-$MeOC_6H_4$
90d-Na Ar = 4-$NO_2C_6H_4$

105a-Na (89%)
105b-Na (96%)
105c-Na (58%)
105d-Na (78%)

para **90a-Na–90c-Na**

106-Na **107-Na**

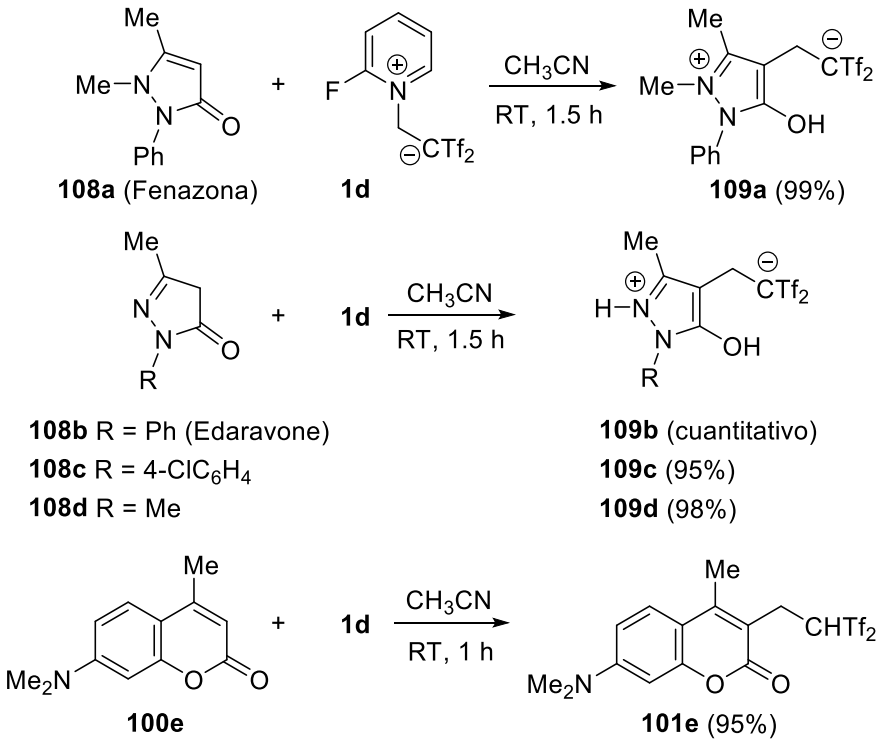
106a-Na/107a-Na (85%; 58/42)
106b-Na/107b-Na (70%; 56/44)
106c-Na/107c-Na (55%; 50/50)

Esquema XII.54

Como productos de estas reacciones se obtuvieron los pirazoles **105a-d** con buenos rendimientos. También se ensayó el alquino no simétrico propiolato de metilo, obteniéndose los correspondientes cicloaductos **106a-c** / **107a-c** tras aplicar condiciones de reacción más fuertes (140ºC en reactor microondas). Desgraciadamente, estos se obtuvieron como mezclas de regioisómeros.

El último reto que nos planteamos fue utilizar nuestra metodología en casos concretos para demostrar sus aplicaciones. Para la industria farmacéutica resulta especialmente interesante la modificación de drogas ya existentes para mejorar su actividad biológica o incluso encontrar nuevas propiedades, sin tener que empezar el desarrollo de un fármaco desde cero. Por ello pensamos que modificar la

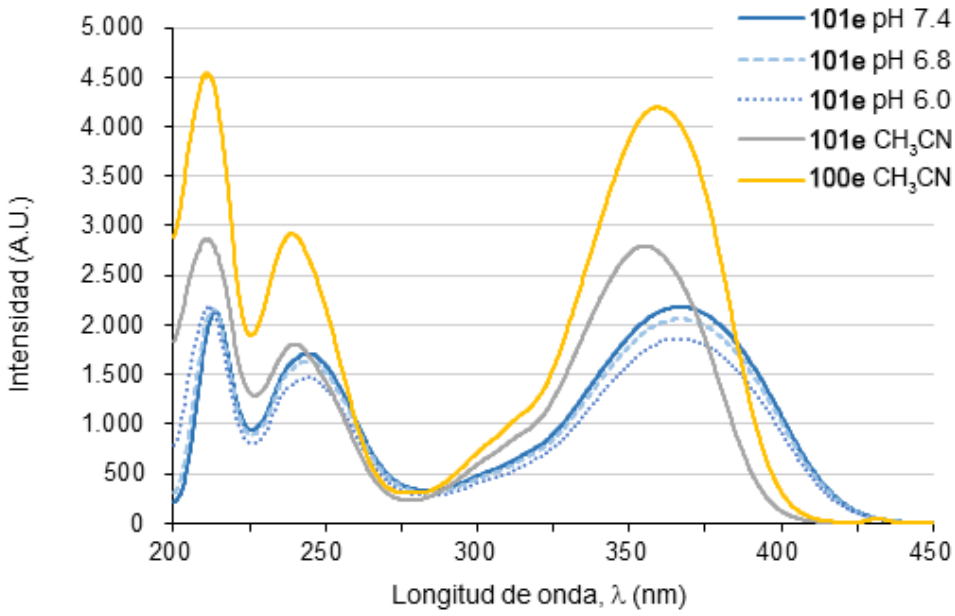
estructura de medicamentos ya presentes en el mercado sería muy interesante. Para ello seleccionamos dos drogas, la fenazona **108a**, también conocida como antipirina, un antiinflamatorio que es el más antiguo analgésico de acción débil y que ejerce, además, una acción antipirética y propiedades espasmolíticas sobre órganos de tejido muscular liso. El otro principio activo elegido fue la edaravone **108b**, usada para ayudar en la recuperación después de sufrir un ictus y también en el tratamiento de la esclerosis lateral amiotrófica (ELA). Desde un punto de vista químico ambas estructuras son pirazolonas, susceptibles de ser alquiladas con nuestra metodología. Satisfactoriamente, comprobamos que al aplicar las condiciones generales de reacción sobre estas drogas se producía la bis(triflil)etilación esperada, obteniendo las estructuras modificadas **109a** y **109b** con rendimientos excelentes en tiempos cortos de reacción (Esquema XII.55).



Esquema XII.55

Las pirazolonas **108c** y **108d**, estructuralmente relacionadas con la edaravone, también originan los productos alquilados **109c** y **109d** con buenos rendimientos. Se obtuvo el análisis por difracción de rayos X de monocristal para las estructuras **109a**, **109c** y **109d**.

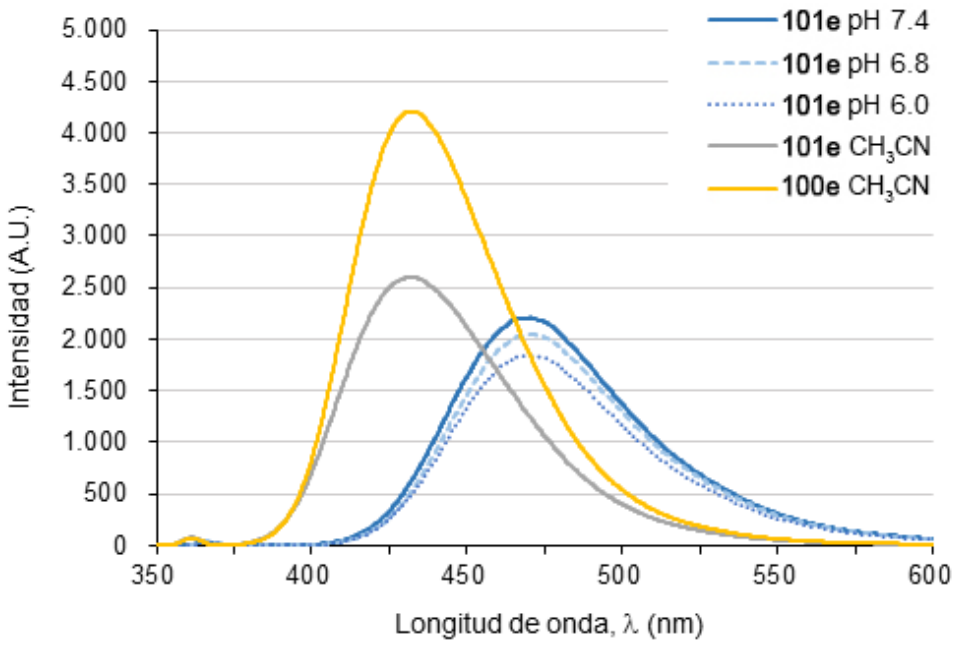
Otra aplicación interesante es la incorporación del resto CH_2CHTf_2 a una molécula con el fin de mejorar su solubilidad en agua. Para ello elegimos la 7-(dimetilamino)-4-metilcumarina **100e** (Esquema XII.55). Esta molécula es un potente colorante azul, que presenta fluorescencia (λ_{ex} = 210 y 359 nm, λ_{em} = 432 nm en acetonitrilo) pero es muy insoluble (<20 μg mL^{-1}) en tampón fosfato 0.1M (pH 6.8 y 7.4) y en agua. Afortunadamente, la reacción de alquilación transcurre sin problemas, obteniéndose el producto **101e** con un 95% de rendimiento.



Espectro corregido, [C] = 5.0 x 10^{-6} mol L^{-1}, 25°C.

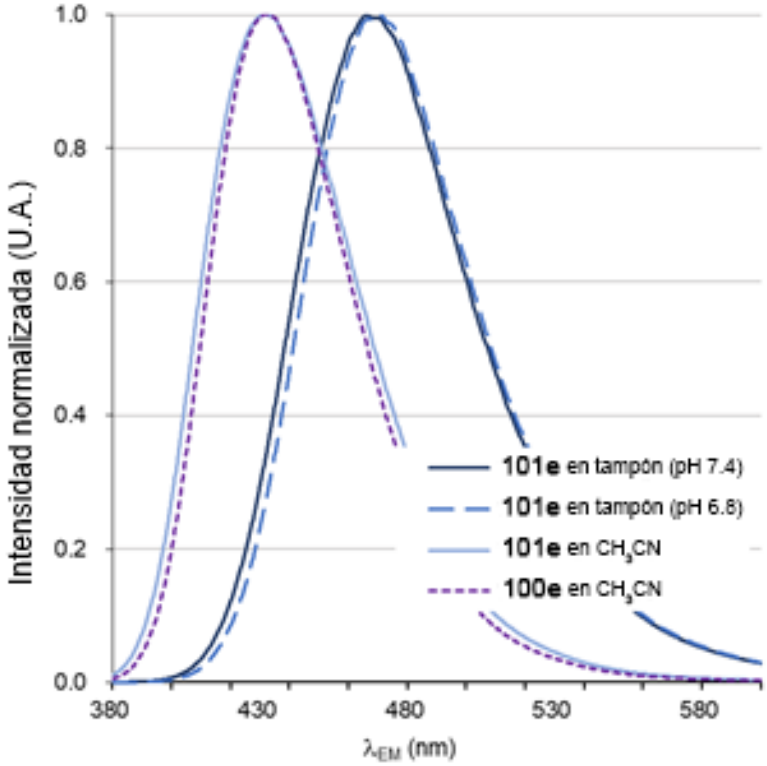
Figura XII.20

Sus propiedades fluorescentes no muestran cambios significativos (λ_{ex} = 210 y 355 nm, λ_{em} = 431 nm en acetonitrilo), ni cambia excesivamente la forma del espectro de excitación de fluorescencia (Figura XII.20), ni la emisión de fluorescencia (Figuras XII.21 y XII.22). Sin embargo, su solubilidad en medio acuoso se ve mejorada, de modo que es posible obtener los espectros de emisión de fluorescencia en disoluciones tampón fosfato (pH 7.4, λ_{em} = 470 nm; pH 6.8, λ_{em} = 471 nm). Las propiedades de fluorescencia apenas afectadas por el cambio estructural y la mejora en la solubilidad, apoyan nuestra hipótesis de que la incorporación del resto CH_2CHTf_2 mejora la solubilidad en agua de compuestos lipofílicos.



Espectro corregido, [C] = 5.0 x 10^{-6} mol L^{-1}, 25°C.

Figura XII.21



Espectro normalizado, longitud de onda de excitación 365 nm, [C] = 5.0 × 10^{-6} mol L^{-1}, [$C_{tampón\ fosfato}$] = 0.1 M, 25ºC.

Figura XII.22

XII.3. Reacciones de zwitteriones de Koshar con dipolos

Para finalizar el presente trabajo se ha llevado a cabo el estudio de reacciones de cicloadición [3+2] entre $Tf_2C{=}CH_2$ y azidas de diferente naturaleza.

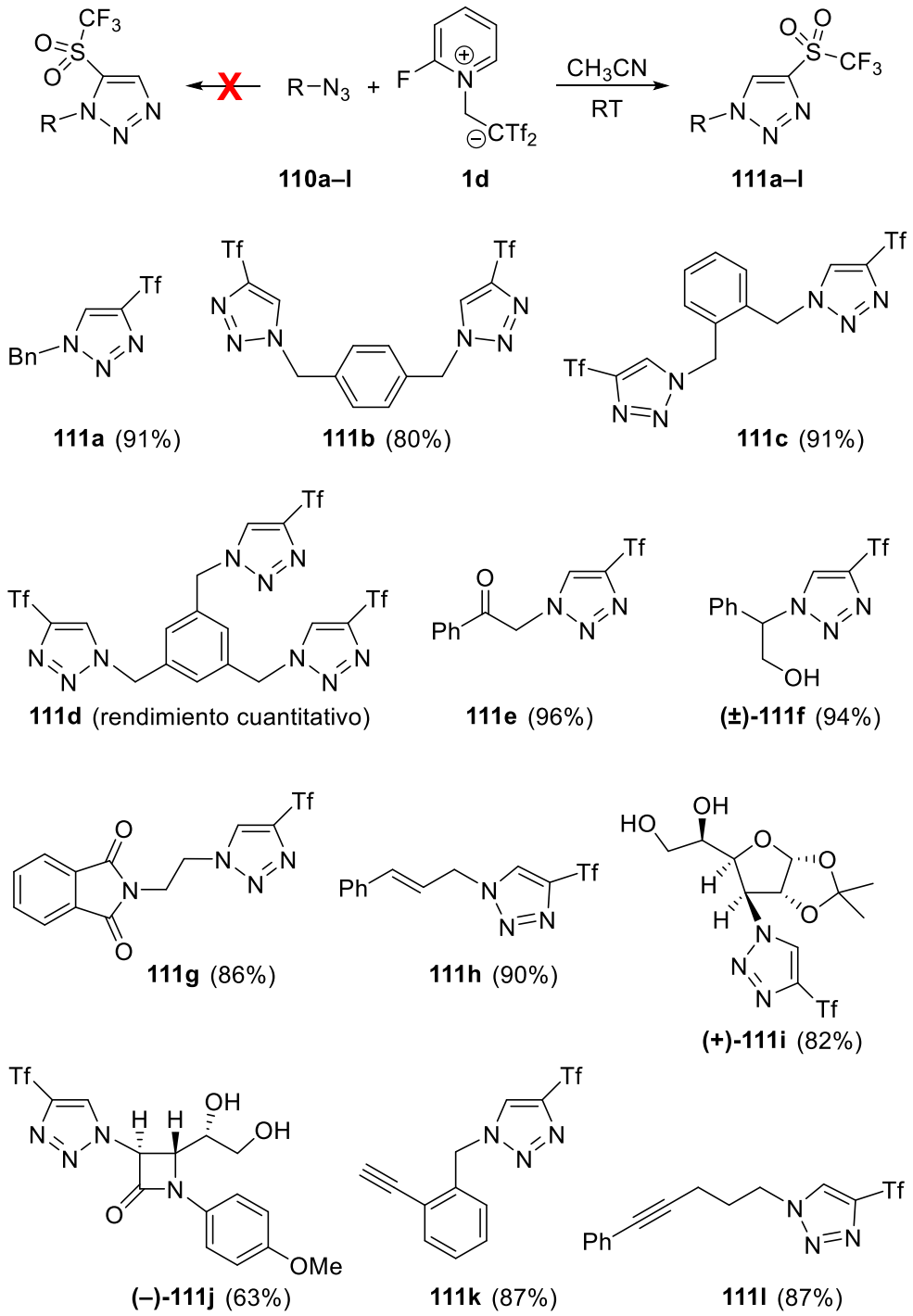
XII.3.1. Capítulo 8: Cicloadición [3+2] de azidas con $Tf_2C{=}CH_2$ sin el uso de metales para la preparación regioselectiva de 4-(trifluorometilsulfonil)-1,2,3-triazoles

Una vez explorada la reactividad del $Tf_2C{=}CH_2$ sobre alquinos y demostrada su utilidad para la preparación de ciclobutenos y ciclobutenonas por cicloadición formal [2+2] (Capítulos 1, 2, 3 y 4), así como de otros productos interesantes en los que un ciclobuteno es el intermedio de reacción (Capítulo 5), nos preguntamos si sería posible enfrentar el reactivo $Tf_2C{=}CH_2$ a otras moléculas polarizadas para obtener nuevos compuestos cíclicos.

Para ello, escogimos como materiales de partida azidas orgánicas, cuyo grupo azido es un grupo funcional muy versátil en Síntesis Orgánica y que entre su rica reactividad se encuentra la posibilidad de llevar a cabo cicloadiciones [3+2].

Partiendo de la experiencia adquirida en los trabajos anteriores se emplearon las condiciones generales que tan buenos resultados han dado para activar la reactividad de los zwitteriones de Koshar. Se aplicaron estas condiciones a la bencilazida **110a** como sustrato modelo. Dichas condiciones consisten en utilizar acetonitrilo como disolvente a temperatura ambiente, así como azida y zwitterión en cantidades equimolares. Aun así, se procuró llevar a cabo un proceso de optimización en el que se combinaron diferentes temperaturas y disolventes, pero en ningún caso se mejoraron los resultados. La reacción sobre el sustrato **110a** condujo a la obtención del *C*-triflil-triazol **111a** con excelente rendimiento. Sorprendentemente, como se comentó en los Antecedentes Generales, no existe en la literatura ningún procedimiento descrito para la obtención de este tipo de triazoles. Además, los ensayos de escalado sobre la azida **110a** demostraron la posibilidad de obtener su triazol correspondiente sin erosionar el rendimiento.

Establecidas las condiciones optimizadas, las aplicamos a diferentes azidas alifáticas **110** obteniéndose sus correspondientes triazoles **111** (Esquema XII.56).



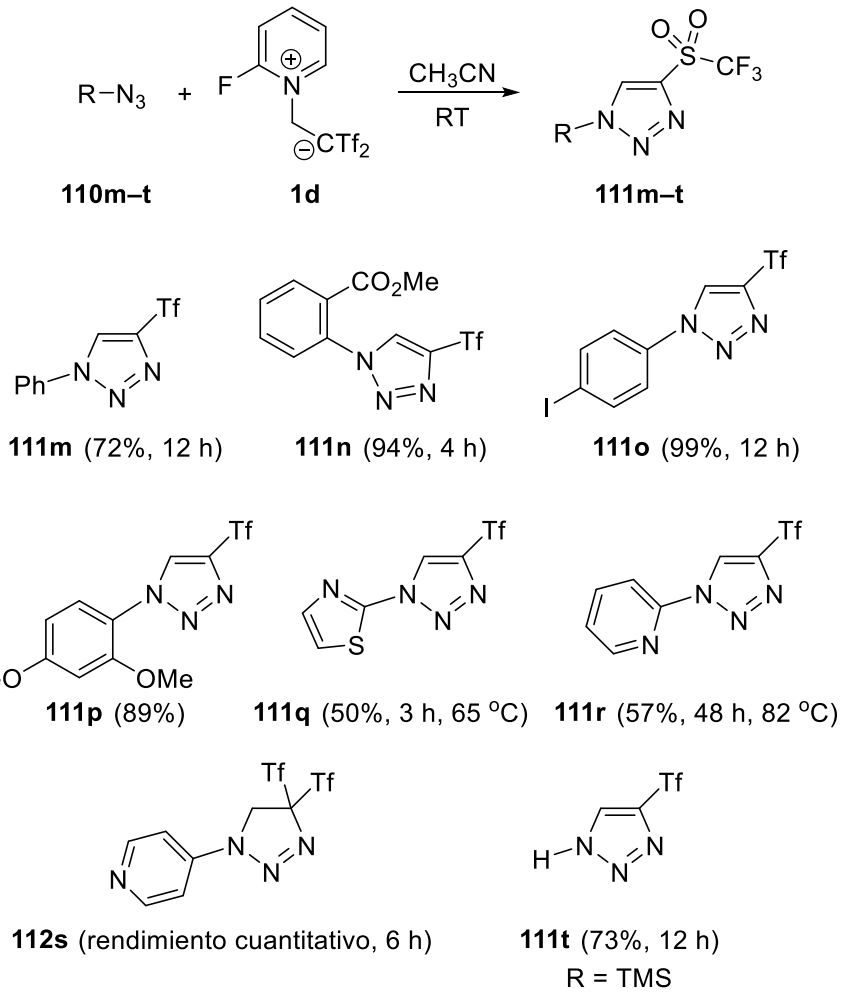
Esquema XII.56

Hay que destacar que las azidas de partida **110** elegidas se encuentran engarzadas en moléculas con diferentes grupos funcionales sensibles, ello con el fin de conocer el alcance y la quimioselectividad del protocolo sintético. Así fue posible obtener los *C*-triflil triazoles **111a-l** con excelente rendimiento. El uso de diazidas **110b** y **110c** y la triazida **110d** permiten la obtención de bis- y tris(triazoles)

respectivamente. Además, la suavidad de las condiciones permite su aplicación a las azidas enantiopuras **110i** y **110j** sin que la estereoquímica de los centros se vea afectada y con unos rendimientos razonables.

La quimioselectividad queda demostrada también a través de la aplicación del protocolo a las azidas **110h**, **110k** y **110l**, pues ni el doble enlace ni los triples enlaces se ven afectados bajo estas condiciones. El grupo carbonilo de la azida **110e** y el hidroxilo en **110f** también son inertes en estas condiciones de reacción, pues no se observa la generación de subproductos como demuestran sus excelentes rendimientos.

Junto con su buena quimioselectividad, el método evita el uso de metales y además, su aplicación no queda limitada solo a azidas alifáticas sino que también puede usarse en azidas aromáticas. Los *C*-triflil triazoles **111m-r** recogidos en el Esquema XII.57 son prueba de ello.



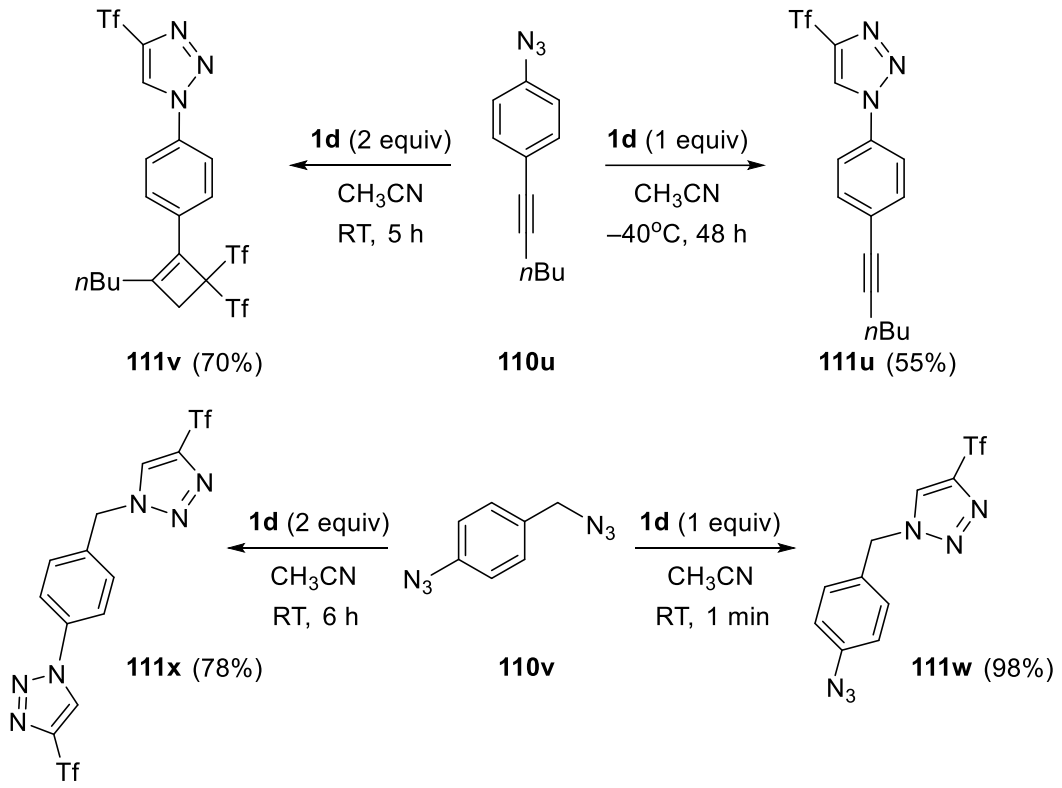
Esquema XII.57

Mientras que las reacciones con azidas alifáticas **110a-l** son instantáneas, con las azidas **110m-s** se necesita un intervalo de tiempo de varias horas para completar la conversión, como se indica en el Esquema XII.57. Solo la azida aromática **110p** con un arilo rico en electrones es capaz de reaccionar instantáneamente, mientras las azidas heteroaromáticas **110q** y **110r** también conducen a los 4-triflil-triazoles **111q** y **111r** pero requiriendo tiempo y calentamiento.

La azida **110s** origina como único producto la dihidro-bis-triflil piridina **112s**. No fue posible la obtención del aducto aromático esperado **111s** ni siquiera aplicando tratamientos posteriores al producto **112s**.

Aunque la la trimetilsilil azida **110t** no es una azida aromática se encuentra en el Esquema XII.57 por compartir con estas un tiempo de reacción semejante. El triazol **111t** obtenido es interesante pues en las mismas condiciones de reacción es posible obtener directamente el núcleo de 4-triflil-triazol con un NH-libre.

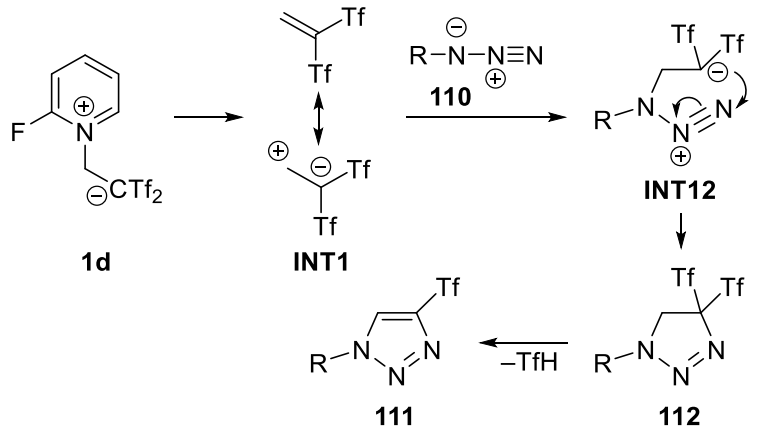
Una vez adquirido el conocimiento necesario acerca de las características que presentan azidas aromáticas y alifáticas en su reactividad, así como del grupo funcional alquino estudiado en trabajos anteriores, nos propusimos aprovechar estas diferencias para funcionalizar selectivamente diferentes posiciones dentro de una misma molécula (Esquema XII.58).



Esquema XII.58

En las condiciones optimizadas, el ciclobutenil-triazol **111v** se obtiene con buen rendimiento a partir de la alquinilazida **110u**. Sobre este mismo material de partida y jugando con la temperatura (enfriamiento a −40ºC) fuimos capaces de obtener selectivamente el aquiniltriazol **111u** sin afectar el triple enlace. En la bis-azida **110v** se explota la enorme diferencia en velocidad de reacción entre azidas aromáticas y alifáticas para conseguir el mono- **111w** o bis-triazol **111x**. En este caso los cambios de temperatura no son útiles para conseguir selectividad, simplemente controlando con precisión la cantidad de zwitterión **1d** utilizado en cada caso es suficiente para obtener **111w** y **111x** sin observase la formación simultánea de ambos en una mezcla.

El mecanismo propuesto para la formación de los 4-trifluorometilsulfonil 1,2,3-triazoles **111** a partir de la sal de 2-fluoropiridinio **1d** se muestra en el Esquema XII.59.



Esquema XII.59

En un primer momento, el zwitterión **1d** en disolución libera el 1,2-dipolo **INT1** que se encuentra entre dos formas resonantes. En el siguiente paso se produce la cicloadición [3+2] entre el 1,2-dipolo **INT1** y la azida **110** originando inicialmente la especie zwriteriónica **INT12**, que evoluciona por cierre de anillo a la especie de cinco eslabones **112**. El aislamiento del ejemplo **112s** (Esquema XII.57) refuerza la idea del que mecanismo transcurre a través de estos aductos. A la formación del dihidro-1*H*-1,2,3-triazol **112** le sigue la salida de un grupo Tf por eliminación de TfH, desembocando finalmente en el triazol **111**. Posiblemente, la fuerza impulsora del proceso sea esta última etapa irreversible, pues la formación del triazol implica la aromatización del anillo.

XIII. CONCLUSIONES

XIII. CONCLUSIONES

El trabajo de investigación recogido en la presente Memoria ha pretendido contribuir al conocimiento sobre la reactividad de los zwitteriones de Koshar, que fueron considerados como una mera curiosidad estructural y se ignoró su utilidad sintética durante años. Este Trabajo ha sido el punto de inicio para una nueva línea de investigación en Síntesis Orgánica. El uso de la molécula altamente polarizada $Tf_2C{=}CH_2$, generada *in situ* a partir de los zwitteriones de Koshar, combina varias características muy deseadas en cualquier reacción: quimioselectividad, regioselectividad, catalizadores e irradiación innecesarios, condiciones suaves y procedimientos experimentales sencillos, permitiendo la preparación de estructuras de difícil acceso por otras vías. Las principales conclusiones de este estudio se resumen a continuación:

1. Se ha demostrado la utilidad del zwitterión de Koshar derivado de la 2-fluoropiridina para la síntesis de ciclobutenos. Liberada en el medio de reacción, la molécula altamente polarizada $Tf_2C{=}CH_2$ se comporta como un 1,2-dipolo cuando se enfrenta a alquinos, dando lugar a una reacción de ciclación [2+2]. La gran ventaja de este método es la facilidad con la que se obtiene de manera totalmente regioselectiva, quimioselectiva y en condiciones suaves de reacción una estructura altamente tensionada como es el ciclobuteno. Además, la ausencia de catalizadores e irradiación hacen de este método único en su campo.

2. Extendiendo la metodología a alquinos heterosustituidos, hemos estudiado el alcance y cambios que se producen en la reactividad. La metodología conserva su alta quimio- y regioselectividad, aunque esta última se ve modificada en función del heteroátomo. Tampoco requiere el uso de catalizadores ni irradiación, solo es necesario el uso de la sal de 2-fluoropiridinio como fuente de $Tf_2C{=}CH_2$. Esta potente metodología, que implica una ciclación [2+2], permite la preparación selectiva de ciclobutenos funcionalizados con cloro, bromo, yodo, oxígeno, azufre, selenio, teluro, nitrógeno, fósforo y silicio.

3. El estudio profundo de las inamidas reveló que es posible producir la ciclación [2+2] cuando reaccionan con la molécula $Tf_2C{=}CH_2$, lo que origina regioselectivamente bis(triflil)aminociclobutenos en ausencia de catalizadores y en condiciones suaves de reacción. Cuando el triple enlace de las inamidas está

sustituido por grupos arilo ricos en electrones en la posición *C*-terminal, se produce un cambio en la reactividad. En estos casos, una reacción secuencial de ciclación/hidroxilación origina 2-amino-3-(triflil)ciclobuten-2-enoles. El estudio de la formación de aminociclobutenos con adición de diferentes alcoholes permite acceder a aminociclobutenil éteres. Además, se ha demostrado la utilidad de estos aminociclobutenos funcionalizados, pues pueden utilizarse como precursores para la preparación de cetonas α-amino-β,γ -insaturadas y 3-(triflil)buta-1,3-dien-2-aminas por apertura 4π-electrocíclica.

4. Se ha desarrollado un método regioselectivo para la obtención de ciclobutenonas a partir de yodoalquinos en un solo paso. Este proceso conlleva tres reacciones secuenciales: ciclobutenación del yodoalquino, seguido de acoplamiento cruzado en la posición del yodo vinílico y formación final del grupo carbonilo en el carbono *gem*-bis-triflilo. La utilidad sintética de este protocolo se ha demostrado mediante la obtención de un inhibidor selectivo de ciclooxigenasa II, así como a través de la transformación de algunas de las ciclobutenonas obtenidas en un conjunto diverso de estructuras.

5. Hemos estudiado la reactividad divergente de inonas con la molécula $Tf_2C{=}CH_2$, obteniéndose dos tipos de triflonas-heterocíclicas. La selectividad en la formación de estos dos productos puede controlarse ajustando la temperatura y el disolvente. Mediante este control se han obtenido bis(triflil)flavonas, bis(triflil)tioflavonas, bis(triflil)selenoflavonas, (triflil)benzotiofenopiranos, (triflil)benzoselenofenopiranos, (triflil)vinil-auronas, y (triflil)piranoindoles. Además, basándonos en experimentos de control y captura de intermedios, se han propuesto mecanismos de reacción fuertemente fundamentados. También, debido al interés biológico y farmacológico que presentan las flavonas, se realizaron ensayos de actividad frente a diferentes microorganismos con algunas de las moléculas obtenidas. Varias bis(triflil)flavonas, bis(triflil)tio- y selenoflavonas mostraron una actividad significativa frente a nematodos.

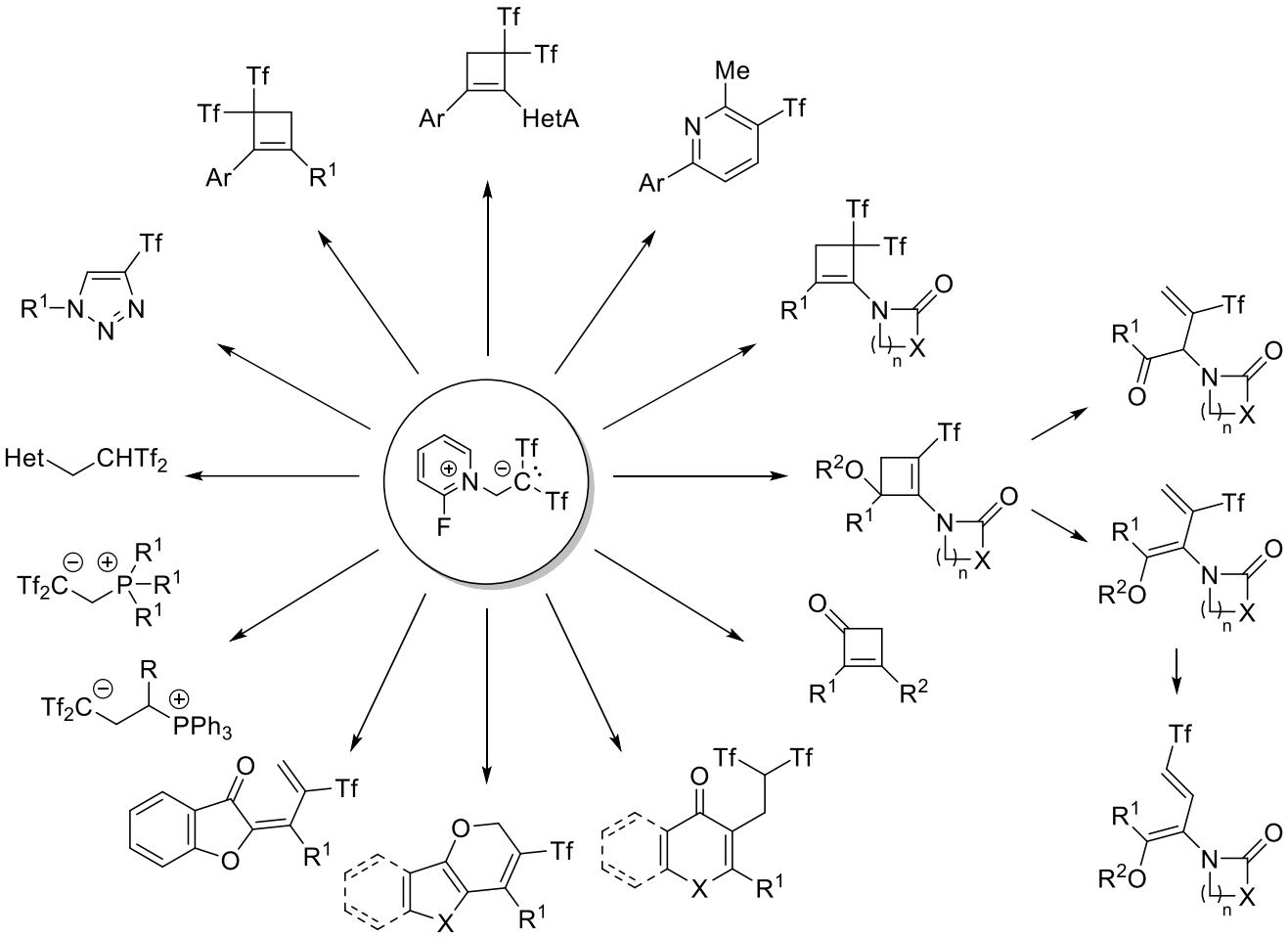
6. Hemos sintetizado satisfactoriamente 1,3- y 1,4-fosfocarbabetaínas usando el reactivo $Tf_2C{=}CH_2$ y fosfinas diferentemente sustituidas. El uso combinado de diferentes técnicas de caracterización, así como el estudio de los datos teóricos computacionales, muestra claramente que no existen interacciones entre los grupos funcionales aniónicos y catiónicos o son extremadamente débiles. Este hecho

también se ha apoyado en el estudio comparativo con una carbabetaína ya descrita, la cual sí presenta fuertes interacciones de transferencia de carga entre las partes aniónica y catiónica. Sin embargo, las carbabetaínas sintetizadas sí que presentan interacciones débiles que sirven para estabilizar la estructura. Basándonos en estos resultados, los productos obtenidos representan el primer ejemplo de carbabetaínas bien definidas. También se ha proporcionado una mayor comprensión acerca de la estabilidad del ion $[Tf_2CR]^-$, en particular se ha estudiado la importancia de la hiperconjugación negativa del par de electrones libre. La influencia de los efectos estéricos en los grupos aniónico y catiónico también se ha estudiado.

7. En ausencia de metales u otros catalizadores, sin necesidad de irradiación hemos conseguido la C−H bis(triflil)etilación de una variedad amplia de heterociclos con una sal de 2-fluoropiridinio. Los productos finales se obtienen mediante una reacción sencilla entre el heterociclo y la molécula $Tf_2C{=}CH_2$. La reacción presenta buena quimio- y regioselectividad. Además, la metodología se ha aplicado para derivatizar diferentes fármacos presentes en el mercado (fenazona y edaravone), así como para aumentar la solubilidad en medio acuoso de un pigmento fluorescente.

8. La aplicación del método de generación *in situ* de la molécula altamente polarizada $Tf_2C{=}CH_2$ a azidas, permite la obtención por primera vez de 4-trifluorometilsulfonil-1,2,3-triazoles. Esta reacción de cicloadición formal [3+2] no requiere el uso de catalizadores u otros aditivos, tampoco irradiación y en una amplia mayoría de casos transcurre a temperatura ambiente. Además, el método presenta una alta quimioselectividad.

El Esquema XIII.1 recoge de manera resumida las posibilidades sintéticas desarrolladas en esta Tesis, a partir del zwitterión de Koshar derivado de la 2-fluoropiridina. Este zwitterión en concreto, también llamado reactivo de Yanai, nos ha posibilitado acceder a una diversidad de estructuras fluoradas en unas condiciones de reacción suaves y con una quimio- y regioselectividad difíciles de alcanzar por métodos alternativos.



Esquema XIII.1

XIV. RESÚMENES

XIV. RESÚMENES

XIV.1. Summary

XIV.1.1. Introduction

Koshar's zwitterions have not been studied since 1976. Fortunately, in 2013 Yanai's group rediscovered them, improving their synthesis and performing a deep analysis of their properties and characteristics.

This work was the starting point of a new research line in our group and has led to the present PhD Thesis. The *in situ* formation of the molecule $Tf_2C{=}CH_2$ in solution, from Koshar's zwitterions, made us consider the study of its behavior and synthetic utility with different unsaturated groups and heterocyclic systems.

On the other hand, the development of cyclization methodologies to obtain highly tensioned rings is of great interest. Cyclobutenes, cyclobutenones and cyclobutenols are included in this group. These four-membered carbocycles are molecules with great synthetic utility but difficult to access; and particularly if their formation is required with chemo-, regio- and stereoselectivity.

Other two kinds of cyclic structures with great importance are the heterocycles flavone and 1,2,3-triazole. Flavones are a class of flavonoids that are a subject of increasing interest because of their biological activities *in vitro* and *in vivo*. The 1,2,3-triazoles have important applications in pharmacology and biological chemistry. Moreover, they are present in many other fields of applied chemistry and they are very versatile synthons in Organic Synthesis.

Futhermore, the synthesis, isolation, characterization and study of the structural properties of stable phospho-carbabetaines is important to extrapolate these data to other betaines that can not be isolated and studied in detail.

From another point of view, since the classic Friedel-Crafts reaction, different alternatives have been sought under milder, metal-free and selective conditions to reach the alkylation of C-H positions in heterocycles. These alkylations are important because they allow to introduce structural modifications to improve some aspect of their properties without affecting others already present.

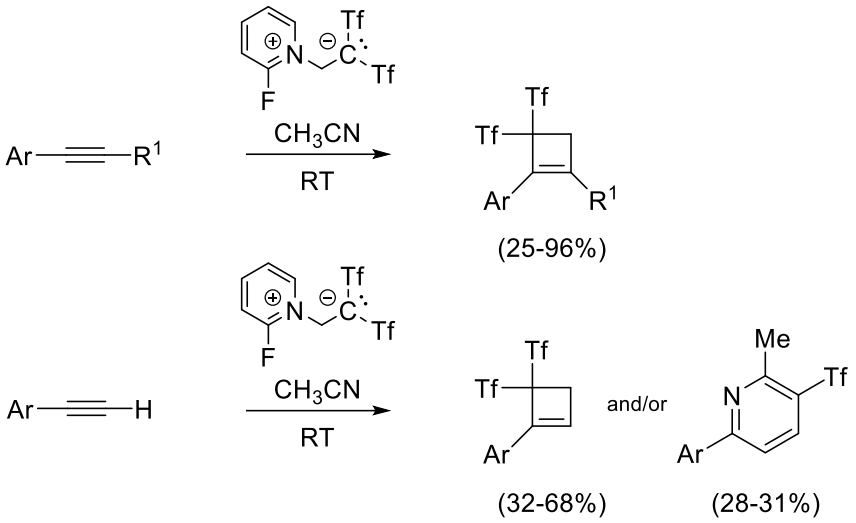
Finally, fluorinated compounds have an important biological activity due to their high lipophilicity and metabolic stability. Therefore, the synthesis of molecules bearing of fluorinated groups is so interesting.

XIII.1.2. Objectives

The aim of this PhD Thesis is to study the synthetic applications of Koshar's zwitterions. The reactivity with unsaturated groups and different heterocycles will be unveiled. In particular, this work has focused on: i) exploring the reactivity with differently substituted alkynes for the synthesis of cyclobutenes, cyclobutenones, cyclobutenols, flavones and fused 2*H*-pyrans; as well as with phosphines to obtain phospho-carbabetaines; ii) to describe a new methodology to produce the selective alkylation of a C-H position in different heterocycles under mild conditions and without the use of metals and irradiation; iii) to study the reactivity with differently substituted azides for the regio- and chemoselective synthesis of 4-(trifluoromethanesulfonyl)-1,2,3-triazoles.

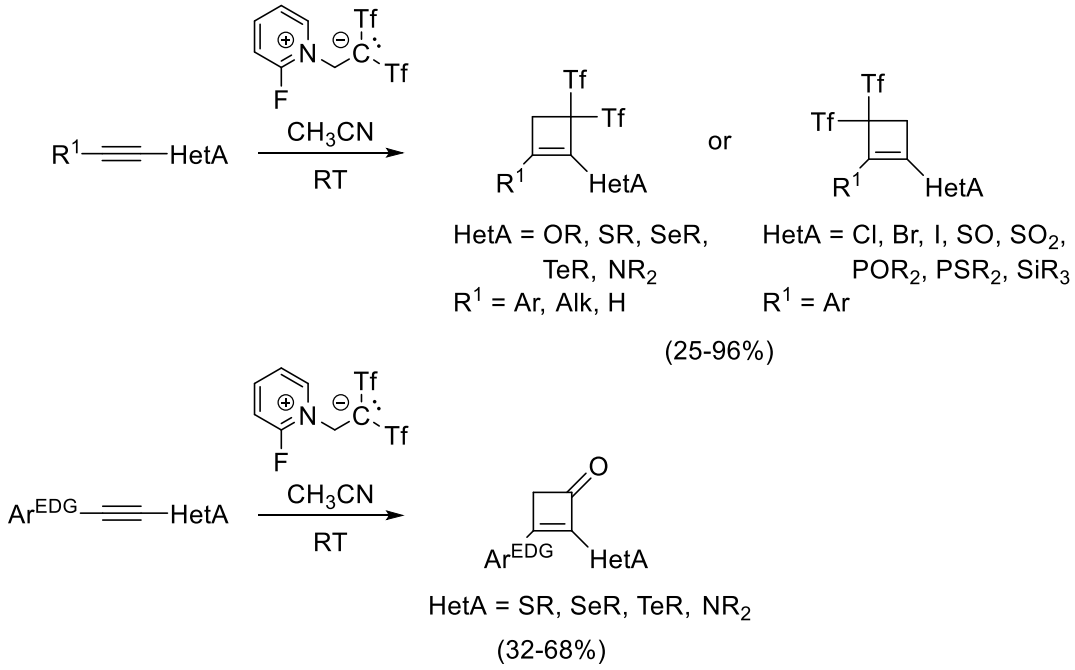
XIII.1.3. Results

First of all, a [2+2] cycloaddition reaction has been described between the molecule generated *in situ* $Tf_2C{=}CH_2$ and differently subtituted alkynes and terminal alkynes. Regarding simple alkynes, bis(triflyl)cyclobutenes were obtained with complete chemo- and regioselectivity. When the same conditions were applied to terminal alkynes, not only the expected cyclobutenes can be obtained, but also, depending on the alkyne substituent, it is possible to obtain pyridines with the participation of the solvent in the reaction. The reactions were carried out at room temperature, without any type of additive or irradiation (Scheme XVI.1).



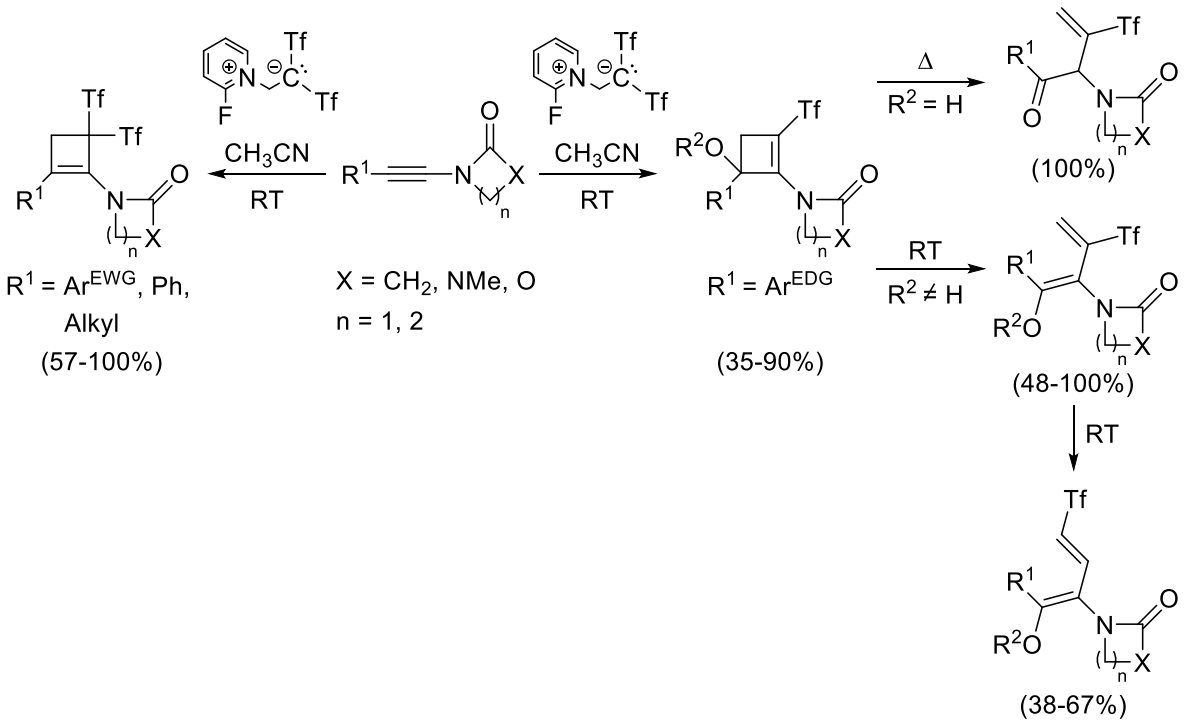
Scheme XIV.1

Extending the previous methodology to heterosubstituted alkynes, scope and changes in the reactivity were checked. The high chemo- and regioselectivity was conserved but the latter is controlled by the electronic effect of the heteroatom. Furthermore, for some specific cases, the reaction leads to cyclobutenones with elimination of triflyl groups through hydration. This powerful methodology has proven to be useful in the selective preparation of cyclobutenes functionalized with chlorine, bromine, iodine, oxygen, sulfur, selenium, tellurium, nitrogen, phosphorus and silicon (Scheme XVI.2).



Scheme XIV.2

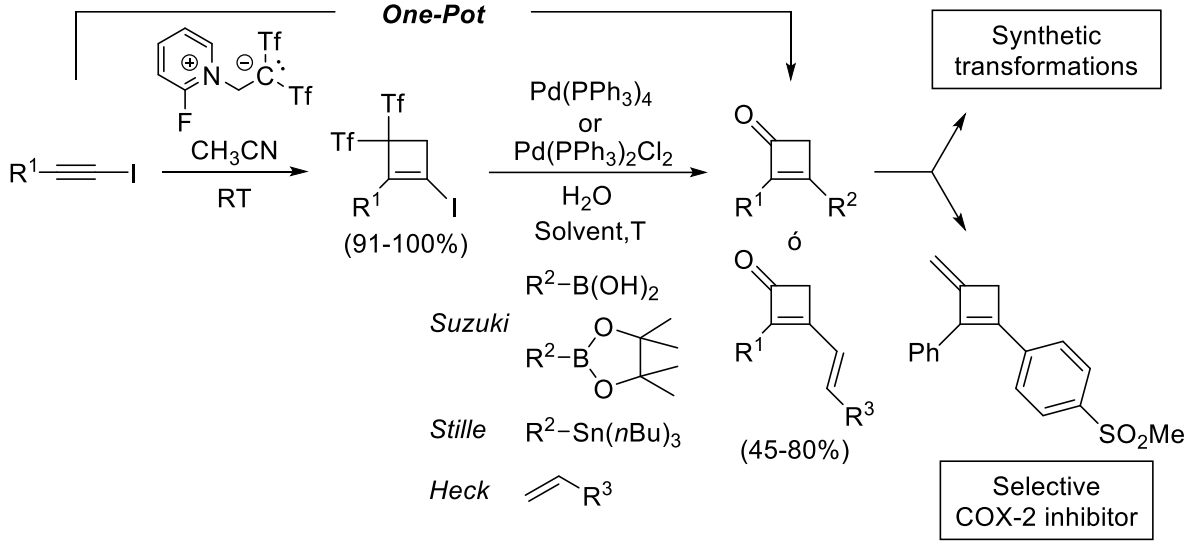
On the other hand, an independent study of nitrogen-substituted alkynes, *i.e.* ynamides was carried out. Depending on the non-nitrogenous substituent of the alkyne we observed two different reactivities. When the substituent is an aryl moiety with neutral or electron-poor groups, cyclobutene formation was achieved as observed in the previous work. However, when the substituent is an electron-rich aryl the reaction incorporates adventitious water, or an alcohol added to the reaction medium, originating cyclobutenols or cyclobutenyl-ethers, respectively. This method is the first preparation of cyclobutenols that does not involve the reduction of a cyclobutenone. These products can be transformed by electrocyclic opening to α-amino-β,γ-unsaturated ketones and 1,3-butadienes. (Scheme XIV.3).



Scheme XIV.3

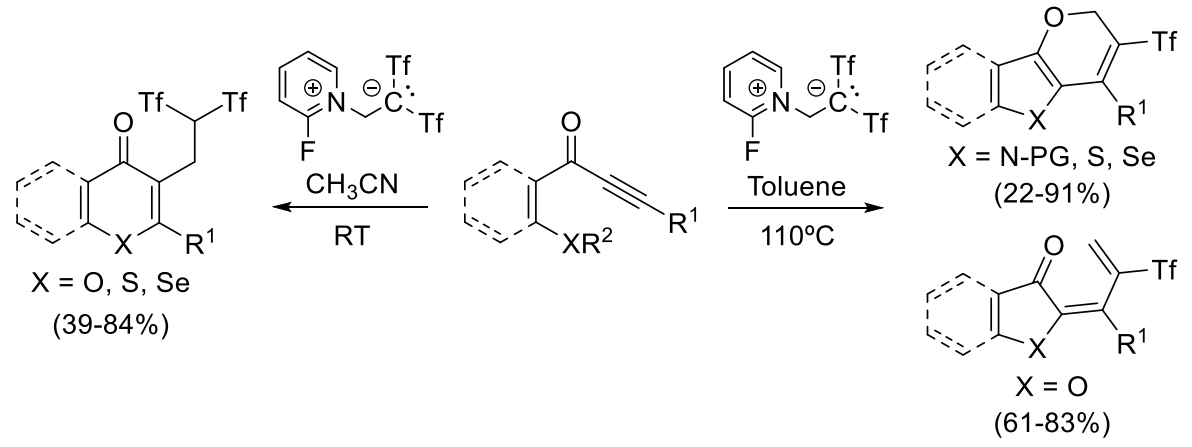
Furthermore, we have described a novel methodology for the one-pot synthesis of cyclobutenones from iodoalkynes. The overall process involves the initial formation of iodocyclobutene, followed by palladium-catalysed cross coupling and a final step of hydration with elimination of the triflyl groups. The usefulness of cyclobutenones has been demonstrated by transforming them into a set of very different structures. Likewise, the method has been applied in the synthesis of a

selective inhibitor of COX-2, improving the yield of the original synthetic route (Scheme XIV.4).



Scheme XIV.4

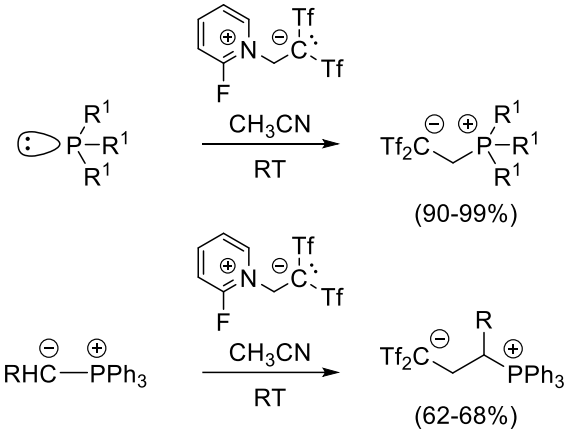
The study of the reactivity on ynones unveiled two divergent reactivities allowing the obtention of flavones and fused 2*H*-pyrans or vinyl-aurones. By adjusting temperature, solvent and the order of addition of the 2-fluoropyridinium salt, it was possible to obtain these products with high selectivity and wide scope. In addition, the isolation of different reaction intermediates allows the proposed mechanism to have a solid empirical base (Scheme XIV.5).



Scheme XIV.5

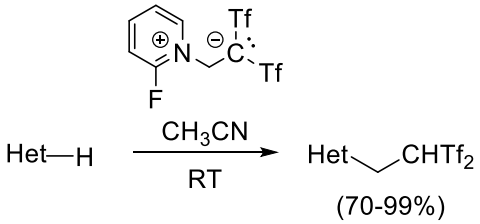
To finish the study of alkynes, we explored the reactivity of alkynyl phosphines. This type of alkyne has a similar behavior to other differently substituted phosphines and phosphorus ylides. By reacting them with the 2-fluoropyridinium salt, *P*-alkylation

occurs providing the 1,3- and 1,4-phosphocarbabetaines. The comparative study with different characterization techniques and computational calculations allowed to know important data about some weak interactions, which collectively serves to stabilize the molecular structure (Scheme XVI.6).



Scheme XIV.6

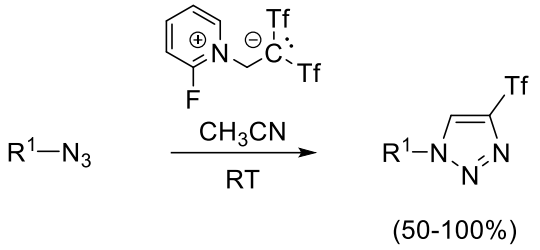
Next, we explored the ability of the molecule generated *in situ* $Tf_2C{=}CH_2$ to operate as a Michael acceptor, similar to the previous phosphine alkylation, for the direct fluoroalkylation of heterocycles. We developed a methodology to achieve selective alkylation with the CH_2CHTf_2 moiety of C-H positions in electron-rich heterocycles (aromatic and non-aromatic rings). This reaction occurs under mild conditions, without catalyst nor irradiation. The utility of this methodology was demonstrated with the alkylation of two comercial drugs, as well as with a fluorescent pigment to increase its solubility in water without affecting its luminescent properties (Scheme XIV.7).



Het = indole, pyrrole, oxazole, thiazole, imidazole, tetronate, coumarin, benzofuran, 1*H*-pyrazole, 1*H*-pyrazol-3-one and sydnone

Scheme XIV.7

Finally, the behavior of differently substituted azides after exposure to $Tf_2C{=}CH_2$ was studied. This study leads to develop a methodology to synthesize for the first time 4-(trifluoromethylsulfonyl)-1,2,3-triazoles. The reaction is highly chemo- and regioselective and is carried out under mild conditions, without additives or irradiation. In addition, the difference reactivity between aromatic/aliphatic azides and alkynes allows the selective formation of triazoles or cyclobutenes within the same molecule (Scheme XIV.8).



Scheme XIV.8

XIV.1.4. Conclusions

In this PhD Thesis, different cyclization and functionalization reactions of alkynes, phosphines, heterocycles and azides have been developed using a 2-fluoropyridine-based Koshar's zwitterion.

The methodology described herein presents remarkable examples for the efficient and selective construction of highly strained rings, flavones, fused 2*H*-pyrans and 1,2,3-triazoles, through simple, chemo- and regioselective processes.

Using the same reaction conditions, it has been possible to produce selectively *P*-alkylation in phosphines and C-H alkylation in heterocycles with the CH_2CHTf_2 moiety.

These reactions have in common the use of mild reaction conditions in a metal/catalyst-free protocol (except in the case of cyclobutenones). Irradiation is not necessary and all substrates are easily accessible. In addition, fluorinated groups have been incorporated simultaneously in all products.

In some specific cases, the methodologies developed have been applied for the preparation of compounds with biological activity, as well as to introduce late stage modifications in drugs and to improve the solubility of a pigment.

XIV.2. Resumen

XIV.2.1. Introducción

Desde el año 1976, los zwitteriones de Koshar no habían vuelto a ser estudiados. En 2013, el grupo de Yanai y colaboradores los redescubren, mejorando su síntesis y analizando profundamente su estructura y propiedades.

Este trabajo sentó las bases para la línea de investigación desarrollada por nuestro grupo de investigación y que ha dado lugar a la presente Tesis. La fácil formación *in situ* de la molécula $Tf_2C{=}CH_2$ en disolución, a partir de los zwitteriones de Koshar, hizo que nos planteáramos estudiar su comportamiento y utilidad sintética frente a diferentes sistemas insaturados y heterociclos.

Por otro lado, el desarrollo de metodologías de ciclación para obtener anillos altamente tensionados tiene gran interés. En este grupo de compuestos se engloban los ciclobutenos, ciclobutenonas y ciclobutenoles; moléculas con gran utilidad sintética, pero de difícil acceso, más si se requiere su formación de manera quimio-, regio- y estereoselectiva.

Otras estructuras cíclicas de gran importancia son los heterociclos de flavona y 1,2,3-triazol. El primero, ha levantado en los últimos años gran interés debido a la actividad biológica que presenta *in vitro* e *in vivo*. El segundo, aparte de sus aplicaciones en farmacología y química biológica, está presente en otros muchos campos de la química aplicada y es un sintón muy versátil en síntesis.

Por otro lado, la síntesis, aislamiento, caracterización y estudio de las propiedades estructurales de fosfo-carbabetaínas resulta importante para extrapolar esos datos a otras betaínas que no pueden aislarse y estudiarse en detalle.

Por otra parte, desde la reacción clásica de Friedel-Crafts se han buscado alternativas en condiciones más suaves, libres de metales y selectivas para alquilar posiciones C−H en heterociclos. Estas alquilaciones son importantes, pues permiten introducir modificaciones estructurales para mejorar algún aspecto de sus propiedades sin afectar a otras ya presentes.

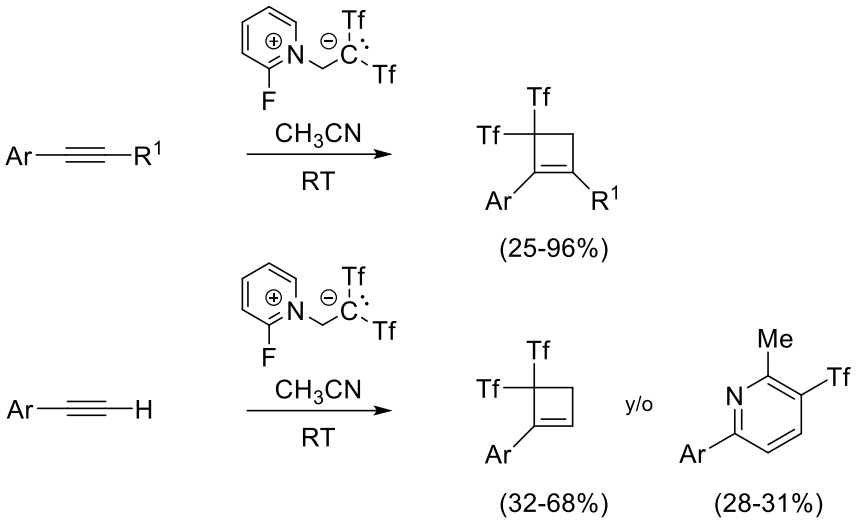
Finalmente, los compuestos fluorados presentan una importante actividad biológica gracias a su alta lipofilia y estabilidad metabólica. Por ello, la síntesis de moléculas con la introducción de grupos fluorados resulta tan interesante.

XIV.2.2. Objetivos

El objetivo general de esta Tesis Doctoral es estudiar las aplicaciones sintéticas que pueden ofrecer los zwitteriones de Koshar. Se determinará la reactividad que presentan frente a diferentes sistemas insaturados y diversos heterociclos. En particular, el presente trabajo se ha centrado en: i) explorar la reactividad con alquinos de diferente naturaleza para la síntesis de ciclobutenos, ciclobutenonas, ciclobutenoles, flavonas y 2*H*-piranos fusionados; así como con fosfinas para obtener fosfo-carbabetaínas; ii) describir una nueva metodología para producir la fluoroalquilación selectiva de enlaces C−H en diferentes heterociclos en condiciones suaves y sin uso de metales ni irradiación; iii) estudiar la reactividad con azidas diferentemente sustituidas para la síntesis regio- y quimioselectiva de 4-(trifluorometanosulfonil)-1,2,3-triazoles.

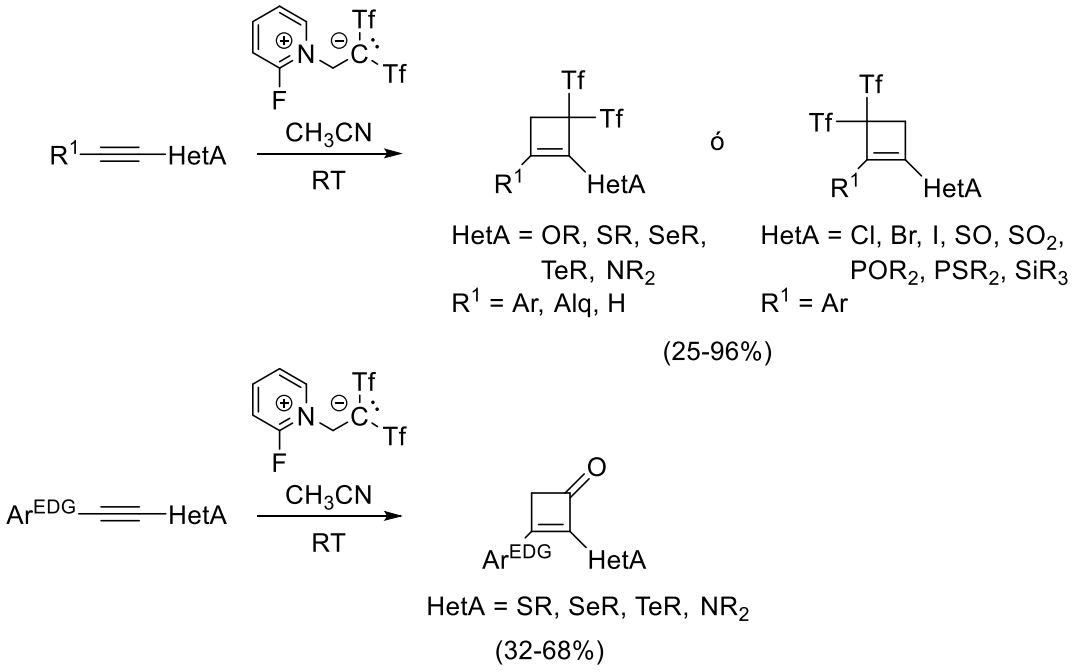
XIV.2.3. Resultados

En primer lugar, se ha descrito una reacción de cicloadición [2+2] entre la molécula generada *in situ* $Tf_2C{=}CH_2$ y alquinos sencillos o sustituidos por restos alquilo y arilo, así como en alquinos terminales. Con los primeros se obtienen bis(triflil)ciclobutenos de manera totalmente quimio- y regioselectiva. Con alquinos terminales no solo pueden obtenerse los ciclobutenos esperados, sino que, modulado por el sustituyente del alquino, es posible obtener piridinas con participación del acetonitrilo (disolvente de la reacción). Ambas reacciones transcurren a temperatura ambiente, sin la necesidad de ningún tipo de aditivo o irradiación (Esquema XVI.1).



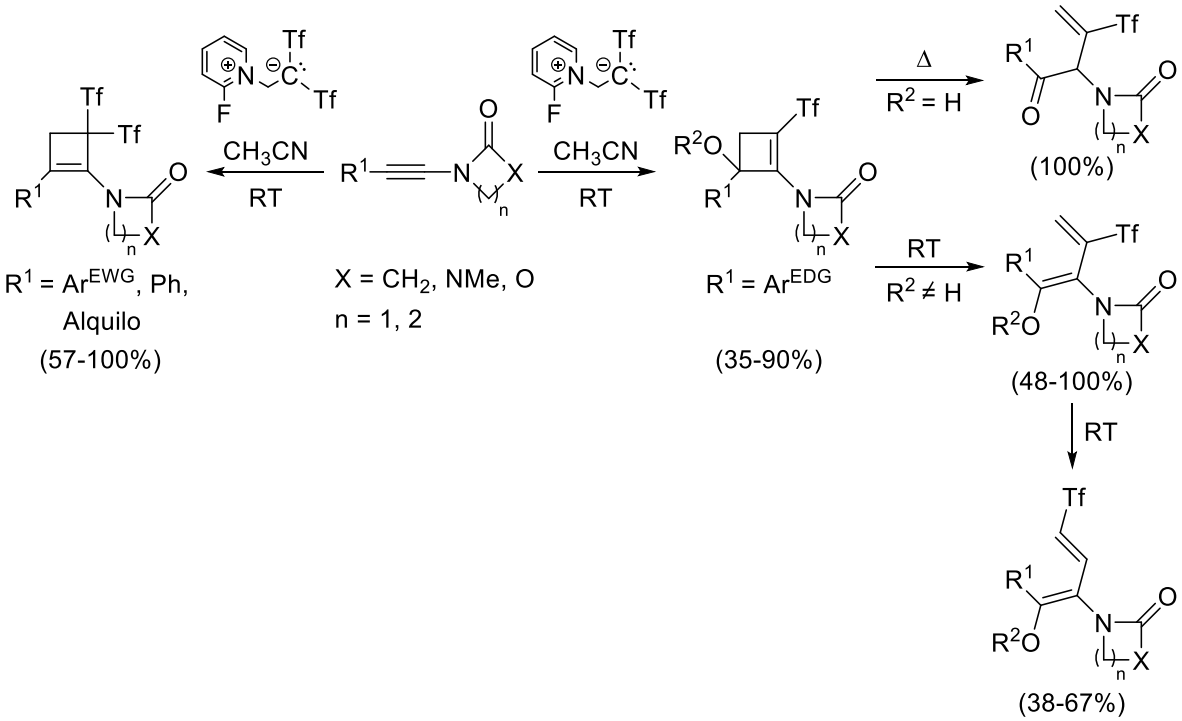
Esquema XIV.1

Extendiendo la metodología anterior a alquinos heterosustituidos, se comprobó el alcance y cambios en la reactividad. Se conserva la alta quimio- y regioselectividad, aunque esta última se ve modificada en función del heteroátomo. Además, para algunos casos concretos, la reacción conduce a las ciclobutenonas, con eliminación de los grupos triflilo. Esta metodología ha demostrado ser útil en la preparación selectiva de ciclobutenos funcionalizados con átomos de cloro, bromo, yodo, oxígeno, azufre, selenio, teluro, nitrógeno, fósforo y silicio (Esquema XVI.2).



Esquema XIV.2

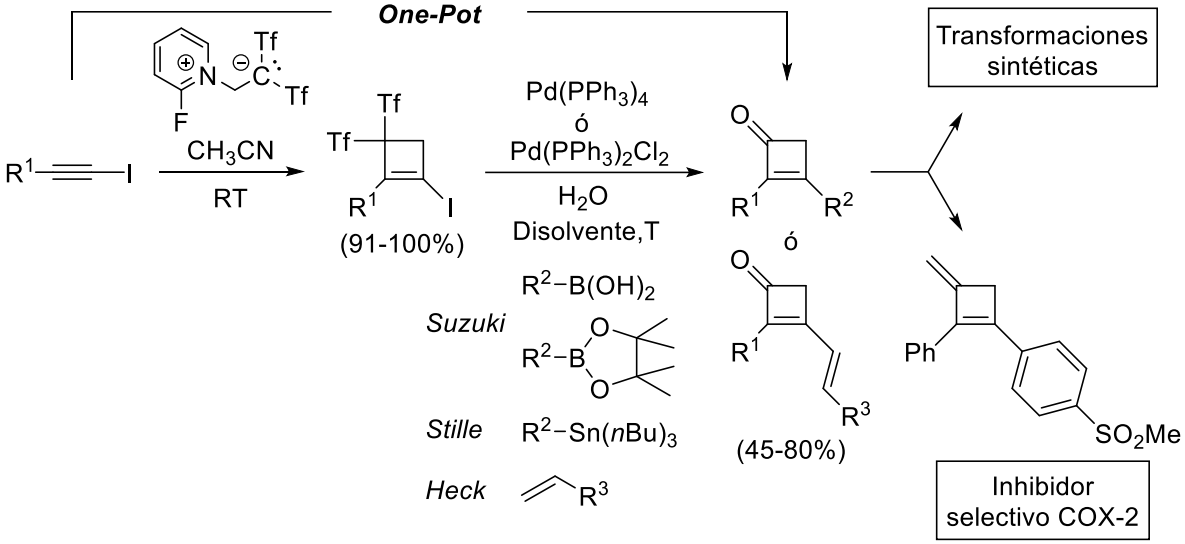
Por otro lado, se llevó a cabo el estudio independiente de las inamidas, alquinos sustituidos por grupos nitrogenados. En función del sustituyente no nitrogenado del alquino se observan dos reactividades diferentes. Cuando el sustituyente es un grupo neutro o pobre en electrones se observa la misma reactividad que en el trabajo anterior. Pero cuando el sustituyente es un arilo rico en electrones la reacción incorpora agua presente en el medio, o un alcohol añadido al medio de reacción, originando aminociclobutenoles o aminociclobutenil éteres respectivamente. Este método es el primer ejemplo de obtención de ciclobutenoles en un solo paso que no implica la reducción de una ciclobutenona precursora. Estos productos pueden ser derivatizados por apertura electrocíclica a cetonas α-amino-β,γ-insaturadas y 1,3-butadienos. (Esquema XIV.3).



Esquema XIV.3

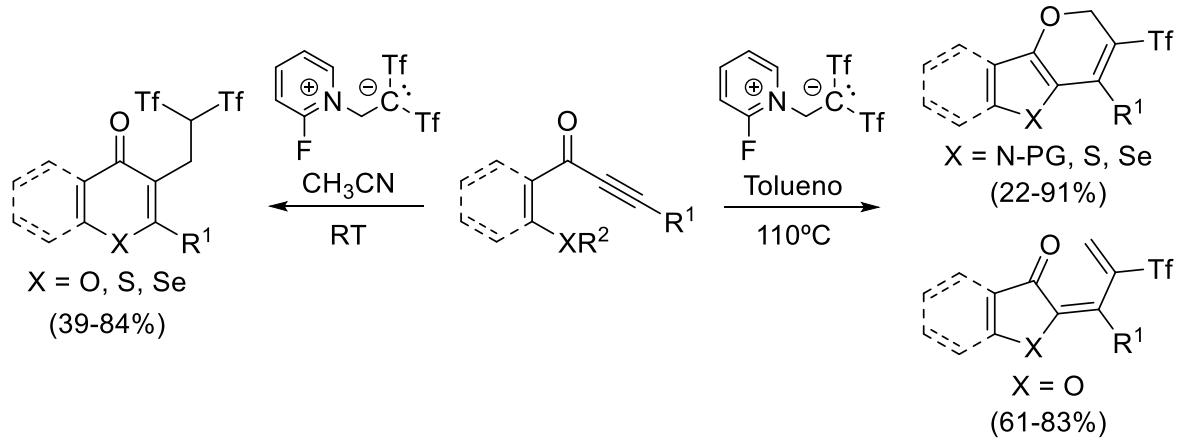
Por otra parte, se ha descrito una metodología novedosa para la síntesis regioselectiva de ciclobutenonas en un solo paso (*one-pot*) desde yodoalquinos. El proceso global implica una primera etapa de formación del yodociclobuteno, seguido del acoplamiento cruzado catalizado por paladio y una etapa final de hidratación con eliminación de los grupos triflilo. La utilidad de las ciclobutenonas ha sido demostrada mediante trasformación de estas en un conjunto de estructuras muy diferentes entre sí. Así mismo, el método ha sido aplicado en la síntesis de un

inhibidor selectivo de COX-2, mejorando sustancialmente el rendimiento de la ruta sintética original (Esquema XIV.4).



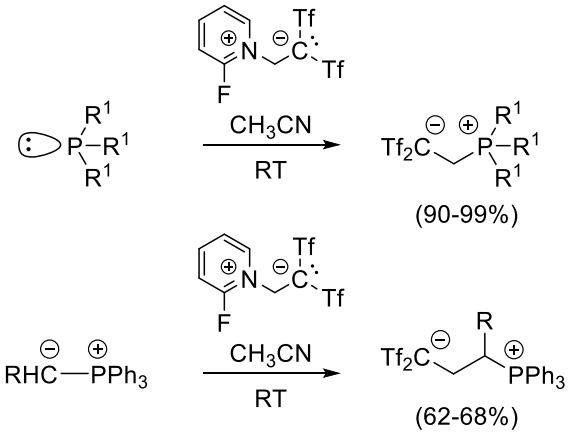
Esquema XIV.4

El estudio de la reactividad sobre inonas desvelo dos reactividades completamente diferentes entre sí y que permiten la obtención de flavonas y 2*H*-piranos fusionados o vinil-auronas. Ajustando la temperatura, el disolvente y el orden de adición del zwitterión de 2-fluoropiridinio es posible obtener estos productos con una selectividad y alcance muy altos. Además, el aislamiento de diferentes intermedios de reacción permite que el mecanismo propuesto tenga una base empírica muy sólida (Esquema XIV.5).



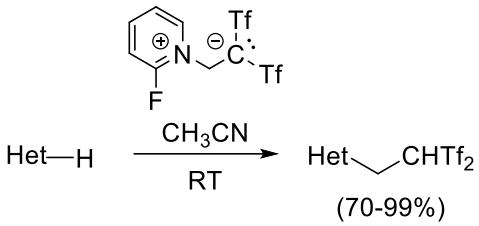
Esquema XIV.5

Finalmente, dentro del estudio de la reactividad de alquinos se estudiaron las alquinilfosfinas. Este tipo de alquino y otras fosfinas diferentemente sustituidas, así como los iluros de fósforo presentan todos ellos un comportamiento similar. Al hacerlos reaccionar con la sal de 2-fluoropiridinio, se produce la *P*-alquilación originando las 1,3 y 1,4-fosfocarbabetainas. El estudio comparativo con diferentes técnicas de caracterización y cálculos computacionales permitió conocer datos importantes sobre diferentes interacciones secundarias que, aunque débiles, ayudan a estabilizar las estructuras (Esquema XVI.6).



Esquema XIV.6

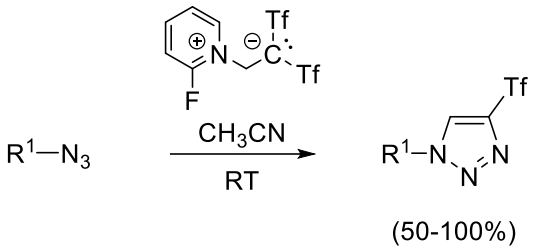
En este Capítulo, exploramos la capacidad de la molécula generada *in situ* $Tf_2C{=}CH_2$ para actuar como un aceptor Michael, de manera similar a lo que ocurría en las fosfinas. Desarrollamos una metodología para lograr la alquilación selectiva con el resto CH_2CHTf_2 de posiciones C-H en heterociclos ricos en electrones (aromáticos y no aromáticos). Esta reacción se produce en condiciones suaves, sin catalizador ni irradiación. La utilidad de la metodología se demostró con la alquilación de dos drogas presentes en el mercado, así como con un pigmento fluorescente, aumentando su solubilidad en agua sin afectar a sus propiedades luminiscentes (Esquema XIV.7).



Het = indol, pirrol, oxazol, tiazol, imidazol, tetronas, cumarina, benzofurano, 1*H*-pirazol, 1*H*-pirazol-3-ona y sidnona

Esquema XIV.7

Por último, se estudió el comportamiento de azidas diferentemente sustituidas frente a la molécula $Tf_2C{=}CH_2$. Este estudio permitió desarrollar una metodología para lograr la síntesis por primera vez de 4-(trifluorometilsulfonil)-1,2,3-triazoles. La reacción es altamente quimio- y regioselectiva y se lleva a cabo en condiciones suaves, sin necesidad de aditivos ni irradiación. Además, la diferencia de reactividad entre azidas aromáticas, alifáticas y alquinos permite la formación selectiva de triazoles y ciclobutenos dentro de una misma molécula (Esquema XIV.8).



Esquema XIV.8

XIV.2.4. Conclusiones

En el presente trabajo se han desarrollado diferentes reacciones de ciclación y funcionalización de alquinos, fosfinas, heterociclos y azidas, haciendo uso en todos ellos de un zwitterión de Koshar en partircular derivado de la 2-fluoropiridina.

Las metodologías descritas representan ejemplos de construcción selectiva y eficiente de nuevos compuestos con anillos altamente tensionados, flavonas, 2*H*-piranos fusionados y 1,2,3-triazoles a través de procesos sencillos, quimio- y regioselectivos.

Utilizando las mismas condiciones de reacción ha sido posible producir la *P*-alquilación y C-H alquilación en fosfinas y heterociclos respectivamente.

Estas reacciones tienen en común el uso de condiciones suaves de reacción, sin el uso de metales u otros tipos de catalizador (excepto en caso de las ciclobutenonas). Tampoco se utiliza irradiación y se parte en todas ellas de sustratos de fácil acceso. Además, en todos los productos se han incorporado simultáneamente grupos fluorados.

En algunos casos concretos se han utilizado las metodologías desarrolladas para la preparación de compuestos con actividad biológica, así como para producir modificaciones en moléculas de actividad conocida y mejorar la solubilidad de un pigmento.

XV. ANEXOS

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Unveiling the uncatalyzed reaction of alkynes with 1,2-dipoles for the room temperature synthesis of cyclobutenes†

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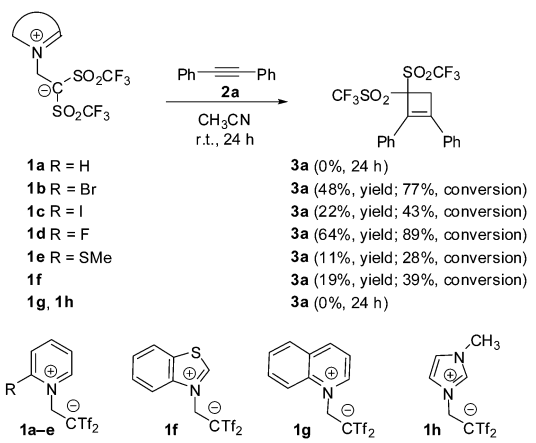
2-(Pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free direct [2+2] cycloaddition reaction of alkynes. Starting from stable zwitterionic pyridinium salts, the electron deficient olefin 1,1-bis(trifluoromethylsulfonyl)ethene is generated *in situ* and immediately reacted at room temperature with an alkyne to afford substituted cyclobutenes. Remarkably, this mild and facile uncatalyzed protocol requires neither irradiation nor heating.

Cyclobutene derivatives are attractive compounds both as target molecules as well as useful building blocks for the construction of more complex structures.[1–7] The most popular method for cyclobutene preparation in a single step is the [2+2] cycloaddition reaction of alkynes with unsaturated systems.[8] The [2+2] cycloaddition of alkynes with alkenes has been studied both under photochemical or thermal conditions as well as by transition-metal catalysis. Because the thermal [π2s + π2s] transformation is a forbidden process according to the Woodward–Hoffmann orbital symmetry principles,[9] in most cases the occurrence of discrete diradical or ionic intermediates has been suggested for both thermal and photoinitiated [2+2] reactions. Despite that, these traditional protocols present serious drawbacks because: (a) modest yields are usually encountered; and (b) either photochemical or strong thermal conditions are required, which may be incompatible with selectivity control as well as sensitive functional groups. Although metal-catalyzed strategies have merged recently, their widespread use in cyclobutene synthesis is precluded due to the narrow substrate scope and moderate selectivity,[10–13] or because of the use of environmentally unsafe or expensive transition-metal salts.[14–17]

Alkynes are useful starting materials for the preparation of a variety of different compounds,[18,19] and when used as reactants in 1,3-dipolar cycloaddition reactions they typically afford five-membered cycles. By analogy, the reaction of alkynes with 1,2-dipoles through a 1,2-dipolar cycloaddition reaction may be a possible solution to produce cyclobutenes with high reaction efficiency.[20] However, this synthetic achievement has not yet been accomplished mainly due to the lack of synthetic methods allowing facile access to 1,2-dipoles. We describe herein the uncatalyzed reaction of alkynes with the 1,2-dipole 1,1-bis(trifluoromethylsulfonyl)ethene, as a straightforward route towards cyclobutenes at room temperature.

In order to achieve a practical and convenient synthesis of cyclobutenes from alkynes, a facile access to the 1,2-dipole partner, namely, the highly polarized $Tf_2C{=}CH_2$ reagent is required. Noticeably, azolium salts **1a–h** (Scheme 1) have been identified as stable precursors of the 1,1-bis(trifluoromethylsulfonyl)ethene species.[21]

1,2-Diphenylethyne **2a** was then selected to test the cyclobutene formation through its reaction with 2-(pyridinium-1-yl)-1,1-bis(triflyl)-ethanide **1a**. Disappointingly, cyclobutene was not formed in the



Scheme 1 Room temperature uncatalyzed synthesis of diphenyl cyclobutene **3a** using differently substituted zwitterions **1**.

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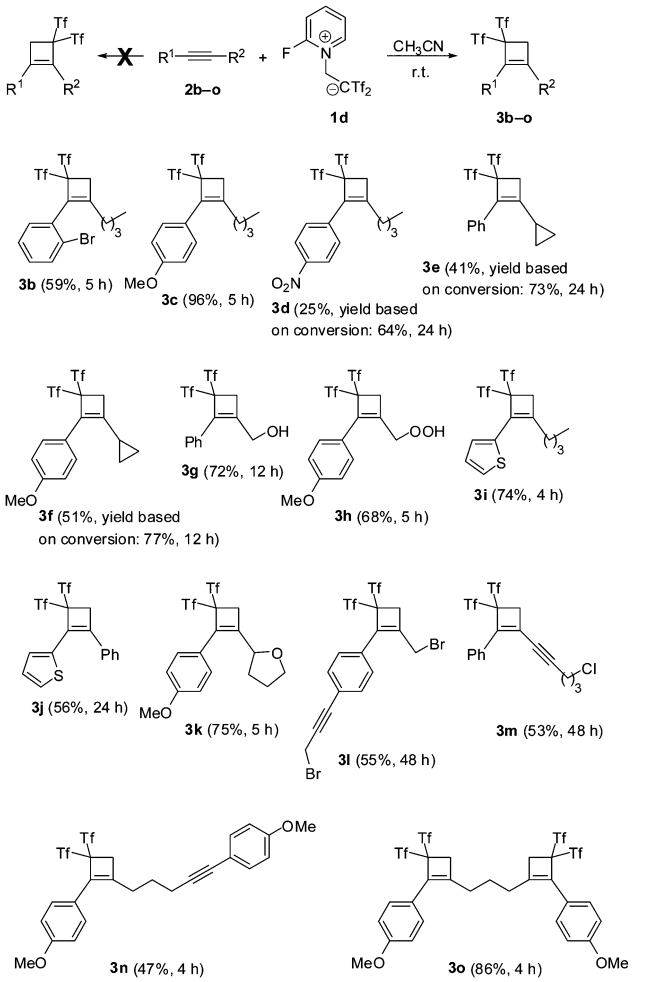
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, computational details, and copies of NMR spectra. CCDC 1007421. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc10111a

event. Much to our delight, modification of the electronic nature of derivative **1** by using differently substituted pyridinium and azolium salts was highly beneficial, because the bromoderivative **1b** gave the cyclobutene **3a** in a fair 48% isolated yield. Even better results (64% yield) were obtained with the fluoropyridinium **1d** (Scheme 1). It is worth noting that the formation of cyclobutene **3a** was successfully carried out at room temperature with no requirements for the catalyst, light or heating sources. The formal [2+2] cycloadditon reaction was optimized in the absence of any additive by systematically changing several reaction parameters. Upon changing the solvent polarity, the efficiency of the reaction changed slightly. Lower reaction yields and recovery of the starting material were observed using DMSO, DMF or THF. It was found that the reaction in the initially selected solvent acetonitrile gave the best results. Among all the temperatures examined, room temperature proved to be the best choice, affording cyclobutene **3a** in a reasonable 64% yield. Finally as observed, the optimal reaction conditions for the cyclobutene formation turned out to be 2-(2-fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1 equiv.) with the appropriate alkyne (1 equiv.), at room temperature in acetonitrile.

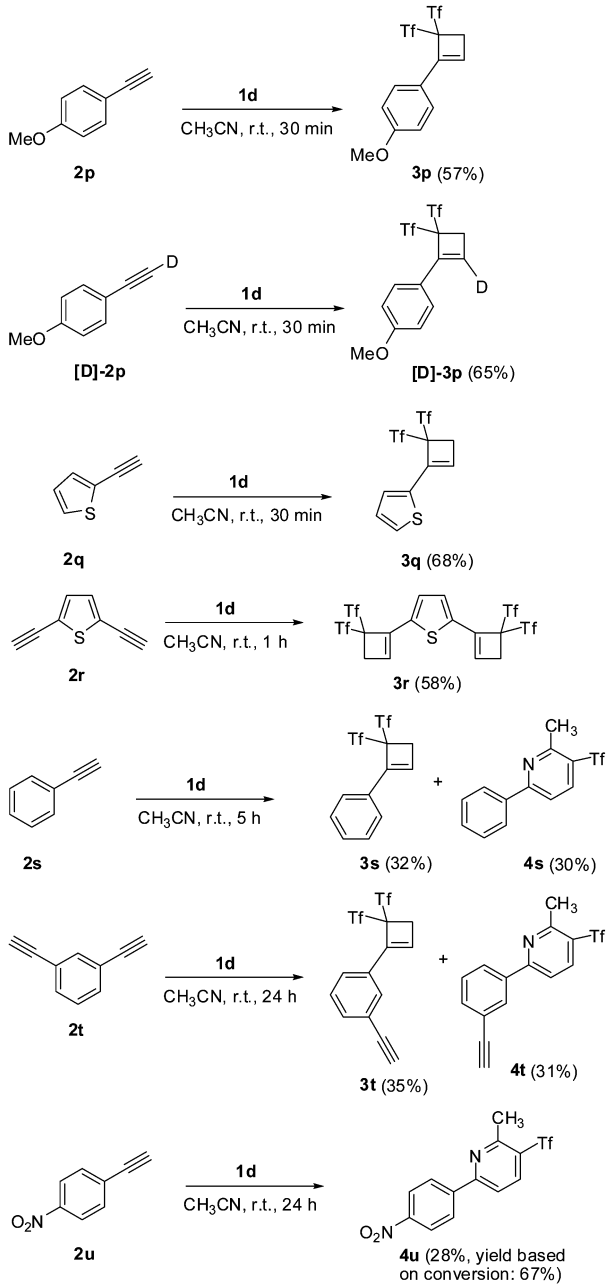
Having identified the optimized reaction conditions we proceeded to study the alkyne scope to further expand the synthetic utility of the process (Scheme 2). A variety of aliphatic, aromatic, and heteroaromatic substituents were well tolerated. Furthermore, non-symmetrical disubstituted alkynes could be successfully used in this intermolecular cyclization reaction. The steric properties of the substituents in the acetylenic moiety did not affect significantly the yield, with 2-aryl functionalized alkyne **2b** performing well in the cyclobutene **3b** formation. The electronic nature of the substituents did appear to have an influence on the course of the reaction. Compared to alkynes having electron-withdrawing substituents, alkynes bearing electron-donating groups gave us better results as far as conversions are concerned. Thus, the electronically-rich methoxy derivative **2c** afforded the corresponding cyclobutene **3c** in much better isolated yield than its nitro counterpart (*e.g.* **2d**). Notably, the regioselectivity was perfect, provided that the substituents at both alkynic sides were different. When a strained cyclopropyl substituent was introduced at the alkyne, the desired cyclobutene still formed (*e.g.* **3e** and **3f**). Interestingly, the mildness of the protocol allows the reaction of internal alkynes phenylprop-2-yn-1-ol **2g** and 1-(3-hydroperoxyprop-1-ynyl)-4-methoxybenzene **2h** bearing sensitive functionalities to be converted into functionalized cyclobutenes **3g** and **3h** in good yields (Scheme 2). Besides alkynes possessing arylacetylene moieties, substrates with heteroaromatic substituents were also investigated. Substrates having a π-excedent heterocycle (*e.g.* **2i** and **2j**) provided the desired cyclobutene (*e.g.* **3i** and **3j**) in good yields (Scheme 2); however, when the thiophene ring was replaced with a π-deficient heterocycle (*e.g.* pyridine), the corresponding cyclobutene was not formed. This phenomenon could be readily understood by considering that an alkyne bearing an electron-rich substituent is more nucleophilic than an alkyne bearing an electron-poor substituent and hence the former is more prone to attack intermolecularly to the nascent zwitterion 1,1-bis(trifluoromethylsulfonyl)ethene. 2-[2-(Aryl)cyclobut-1-enyl]tetrahydrofuran **3k** was also obtained in an efficient manner from alkyne **2k** (Scheme 2). The selective monofunctionalization of



Scheme 2 Room temperature uncatalyzed synthesis of cyclobutenes **3b–o** from differently substituted alkynes **2**.

diynes **2l–n** into cyclobutenes **3l–n** as well as the two-fold reaction to form bis(cyclobutene) **3o** from diyne **2n** were also successfully developed (Scheme 2). Interestingly, the mildness of the protocol allows the control of both the mono and the double reaction of diyne **2n** (Scheme 2). As shown in Scheme 2, the above process in a one-pot operation from readily available alkynes and 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides serves as a general approach towards polysubstituted cyclobutenes. Besides, cyclobutenes **3b–o** could be obtained in good yields and with total regioselectivity. Because cyclobutenes are of high synthetic utility, it was desirable to scale-up the procedure in order to obtain gram quantities. It is worth noting that when we performed a 5 mmol-scale reaction starting from alkyne **2g**, cyclobutene **3g** was isolated in a yield of 77%, which is slightly higher than that achieved at a smaller scale during the scope study. For conclusive assessment of the structure of compounds **3** the X-ray crystallographic analysis of the crystals of cyclobutene **3c** was undertaken (Fig. S1, see ESI†).[22]

Encouraged by the results obtained in our above method, we focused our attention as well on terminal alkynes, which are generally less reactive. Terminal aliphatic alkynes failed to react and the starting material was recovered unchanged under these conditions. However, 1-ethynyl-4-methoxybenzene **2p** and 1-(ethynyl-*d*)-4-methoxybenzene



Scheme 3 Preparation of cyclobutenes **3p–t** and pyridines **4s–u** from terminal alkynes.

[D]-**2p** were subjected to the optimized conditions and the corresponding cyclobutenes **3p** and [D]-**3p** were smoothly formed in satisfactory yields (Scheme 3). Nicely, the presence of a deuterium atom at the terminal end of the alkyne does not affect the efficiency of the reaction, which may allow the synthesis of deuterated cyclobutenes. In a similar manner 2-ethynylthiophene **2q** and 2,5-diethynylthiophene **2r** reacted with 1,1-bis(triflyl)ethanide **1d** to produce cyclobutene **3q** and bis(cyclobutene) **3r** in reasonable yields (Scheme 3). For terminal alkynes, the acetylene moiety with an electron-donating group on the arene exhibited higher reactivity and required shorter time for completion than that of internal alkynes; probably due to steric reasons. The reaction of phenylacetylene **2s** also worked well and provided the product **3s** along with an unexpected product, the pyridine **4s** (Scheme 3).

1,3-Diethynylbenzene **2t** bearing an extra terminal alkyne, also reacted similarly and provided cyclobutene **3t** and pyridine **4t** in a 1 : 1 ratio (Scheme 3). Although there is absence of chemoselectivity for alkynes **2s** and **2t**, it is worth noting that cyclobutenes **3s,t** and pyridines **4s,t** are easily separated, thus providing readily two valuable cyclic products. Interestingly, nitroaryl substitution in the terminal alkyne did alter the reaction, which exclusively yielded the pyridine adduct **4u** (Scheme 3), but considerable amounts of starting alkyne **2u** remained unaffected under the reaction conditions. The formation of pyridines **4** may be explained taking into account the participation of the solvent (acetonitrile) as the coupling partner (see below). These results suggest that for terminal alkynes, the presence of an electron-donating substituent critically influences the formation of the desired cyclobutene.

Density Functional Theory (DFT) calculations were carried out at the PCM(acetonitrile)-M06-2X/6-31+G(d) level to gain more insight into the above described reaction between alkynes and azolium salts **1**.[23] To this end, we considered the reaction involving phenylacetylene (**2s**) and **1d** in the presence of MeCN, which leads to the formation of cyclobutene **3s** and pyridine **4s** in *ca.* 1 : 1 ratio. The corresponding computed reaction profiles are shown in Fig. 1, which gathers the relative free energies computed at 298 K (ΔG_{298}). Our calculations suggest that the process begins with the formation of 1,1-bis(trifluoromethylsulfonyl)ethene (**INT1**) from **1d**. This initial reaction step occurs *via* the transition state **TS1**, associated with the C···N dissociation, with an activation barrier of only 11.9 kcal mol^{-1} in a slightly endergonic transformation (ΔG_R = 4.8 kcal mol^{-1}). The 1,2-dipole nature of ethene **INT1** is confirmed by the NBO-charges computed at both carbon atoms (+0.37 and −0.70 e, respectively).[24] As a consequence, a stepwise [2+2]-cycloaddition reaction with alkyne **2s** is expected to take place. Indeed, we were able to locate on the potential energy surface of the transition state **TS2**, a saddle point associated with the nucleophilic addition of the terminal carbon atom of alkyne **2s** to the positively charged carbon atom of the dipole **INT1**. This C···C bond forming process, which leads to the zwitterionic intermediate **INT2**, proceeds with an activation barrier of 17.6 kcal mol^{-1}. Interestingly, the addition involving the internal carbon atom of the alkyne proceeds *via* **TS2-B** with a much higher activation barrier $\left(\Delta G^{\ddagger}_{298} = 35.7 \text{ kcal mol}^{-1}\right)$, which makes this alternative nucleophilic addition unfeasible at room temperature. This finding explains the extraordinary regioselectivity of the transformation experimentally observed. Finally, cyclobutene **3s** is formed through a ring-closure reaction *via* **TS3**. The ease of this final reaction step becomes evident from the computed high exergonicity (ΔG_R = −28.1 kcal mol^{-1}) and low activation barrier $\left(\Delta G^{\ddagger}_{298} = 3.0 \text{ kcal mol}^{-1}\right)$ associated with this ring-closure.

The formation of pyridine **4s** necessarily involves the participation of the solvent MeCN as a nucleophile. Thus, zwitterion **INT2** is able to react with MeCN to produce the new zwitterionic inter mediate **INT3** *via* **TS4** $\left(\Delta G^{\ddagger}_{298} = 11.6 \text{ kcal mol}^{-1}\right)$ in an exergonic transformation (ΔG_R = −20.1 kcal mol^{-1}). A subsequent ring-closure *via* **TS5** $\left(\Delta G^{\ddagger}_{298} = 11.6 \text{ kcal mol}^{-1}\right)$ leads to the 3,4-dihydropyridine

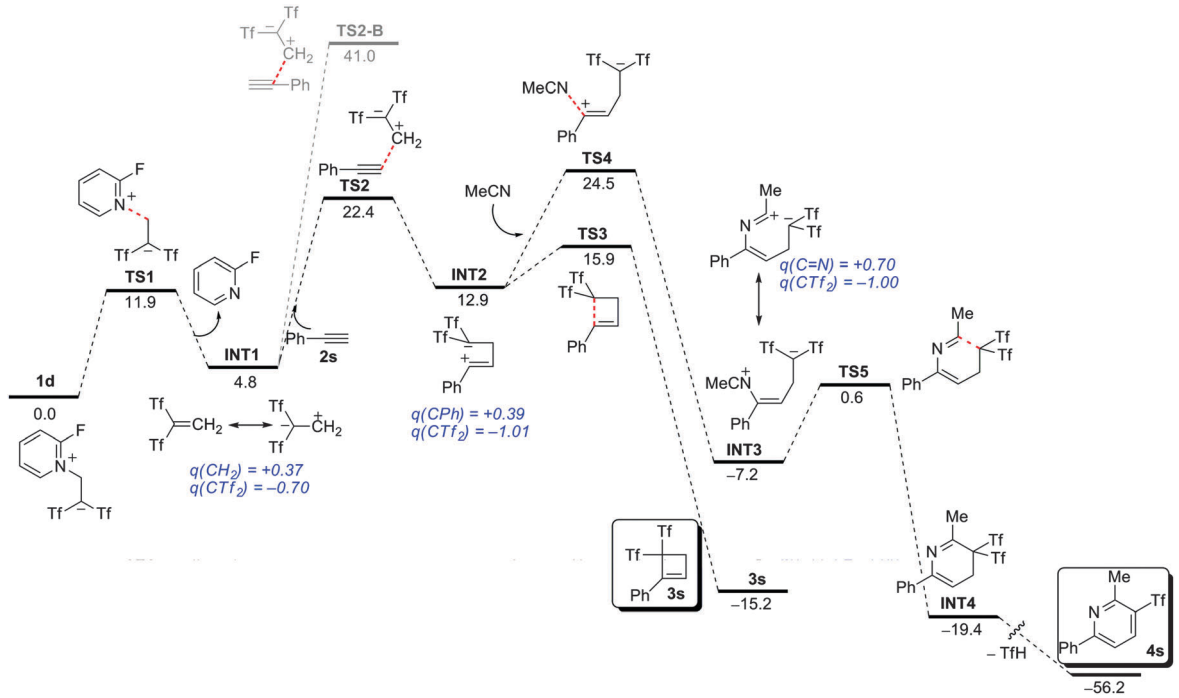


Fig. 1 Computed reaction profile for the reaction between **2s** and **1d**. Relative free energies (ΔG_{298}, at 298 K) are given in kcal mol^{-1}. All data have been computed at the PCM(acetonitrile)-M06-2X/6-31+G(d) level.

INT4, which rapidly evolves to the final pyridine **4s** by TfH elimination in a strongly exergonic transformation (ΔG_R = −49.0 kcal mol^{-1}). The driving-force of this process is clearly related to the gain in aromaticity associated with pyridine formation. Despite that, from the data in Fig. 1 it becomes clear that the stepwise [2+2]-cycloaddition reaction is kinetically favoured over the pyridine formation and for this reason, the exclusive formation of cyclobutenes **3** is observed experimentally in most of the reactions studied (Schemes 2 and 3).

In conclusion, 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free stepwise [2+2]-cycloaddition reaction of alkynes. The great advantage of this method is the easy synthesis of substituted cyclobutenes from readily available and stable precursors under mild conditions. Remarkably, this smooth and facile uncatalyzed protocol requires neither irradiation nor heating. Besides, this protocol has successfully overcome the challenges of earlier methods regarding selectivity of the products.

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Advanced Synthesis & Catalysis

Regioselective Synthesis of Heteroatom-Functionalized Cyclobutene-triflones and Cyclobutenones

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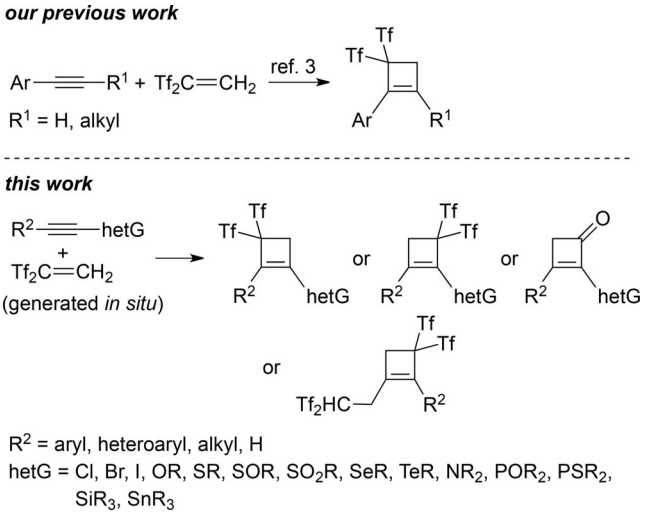
Abstract: The controlled metal-free synthesis of a vast variety of heteroatom-containing cyclobutene-triflones [bis(trifluoromethylsulfonyl)cyclobutenes] and cyclobutenones has been developed starting from heteroatom-substituted alkynes and a pyridinium salt (a latent $Tf_2C{=}CH_2$ source). This powerful methodology, involving cyclization reactions, allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulfur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

Keywords: alkynes; annulation; carbocycles; fluorine; synthetic methods

Introduction

The importance of the synthesis of the cyclobutene core is ever increasing in relation to its presence in natural products and biologically active substances.[1] In addition to its biological importance, this strained carbocycle serves as versatile building block and has attracted considerable attention in organic synthesis.[2] One of the most challenging issues in synthesizing cyclobutenes is how to efficiently and selectivity introduce functionality into the four-membered carbocyclic skeleton. We have recently communicated the cyclization reaction of alkynes and $Tf_2C{=}CH_2$ to afford 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes, but this method was restricted so far to 1-aryl-2-alkyl(aryl)-substituted alkynes.[3] Due to the marked influence on the physical, chemical, and biological properties of small molecules imparted by the presence of heteroatoms, we envisaged the development of a mild method for the preparation of cyclobutene derivatives bearing an extra heteroatom directly linked to an sp^2 carbon atom of the carbocycle (Scheme 1). These heteroatom-substituted cyclobutene-triflones [bis(trifluoromethylsulfonyl)cyclobutenes or bis(triflyl)cyclobutenes][4,5] should bring together the new properties conferred by heteroatoms and the triflyl group with the exceptionally rich chemistry of cyclobutenes.

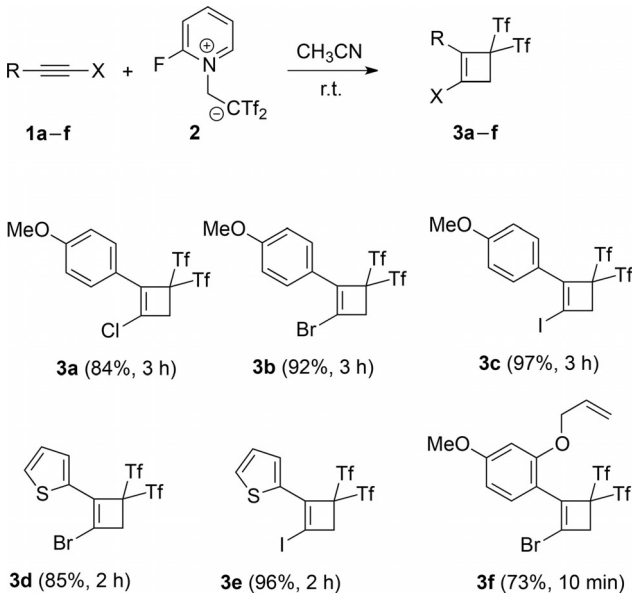


Scheme 1. Metal-free room temperature synthesis of heteroatom-substituted cyclobutene-triflones or cyclobutenones.

Results and Discussion

To explore the effect of various heteroatomic substituents on cyclobutene-triflone formation, several differently functionalized alkynes were selected. 1-Chloroalkyne **1a** was chosen as model substrate to optimize suitable conditions for the reaction with pyridinium salt **2**, a $Tf_2C{=}CH_2$ source. Zwitterion **2** is

poorly soluble in apolar or halogenated solvents, which limited the optimization of the solvent parameter. Acetonitrile at room temperature was identified as the best choice for the reaction of 1-chloroalkyne **1a** with **2**. Notably, the reaction of **1a** with **2** led to bis(trifluoromethylsulfonyl)chlorocyclobutene **3a**, which was obtained in good yield (84%) as single regioisomer without the requirement of any catalyst (Scheme 2). Addition of H_2O may be beneficial by



Scheme 2. Controlled preparation of bis(trifluoromethylsulfonyl)halocyclobutenes **3**.

enhancing the solubility of the zwitterionic reagent **2**. However, when the reaction was carried out in a mixture of acetonitrile/water (1:1), chlorocyclobutene **3a** was obtained in decreased yield (70%). We further investigated the effect of different halogens on the cyclization as shown in Scheme 2. Reaction of 1-bromo(iodo)alkynes **1a–f** with $Tf_2C{=}CH_2$ afforded cycloadducts **3b–f** as sole products in 73–97% yields. Electron-rich substituents accelerated the reaction progress, as exemplified with the formation of bromocyclobutene-triflone **3f** in just 10 min. The structure and regiochemistry of compound **3d** was unambiguously assigned through its X-ray crystallographic analysis (Figure 1).[6]

With the best halocyclobutene-triflone formation conditions identified, the scope of this transformation was then examined in alkynyl ethers, thioethers, selenoethers, and telluroethers **4**. Cyclization adducts **5a–d** could not be obtained at room temperature in reasonable yield because ynol ethers **4a–d** quickly reacted in contact with zwitterion **2**, resulting in a complicated reaction. Fortunately, the reactions were more effective at 0 °C, and ynol ethers **4a–d** underwen smooth cyclization to afford cyclic enol ethers **5a–d** in

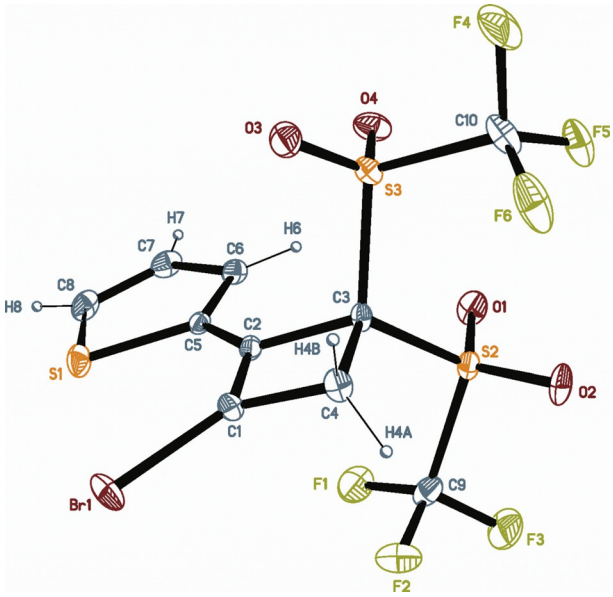
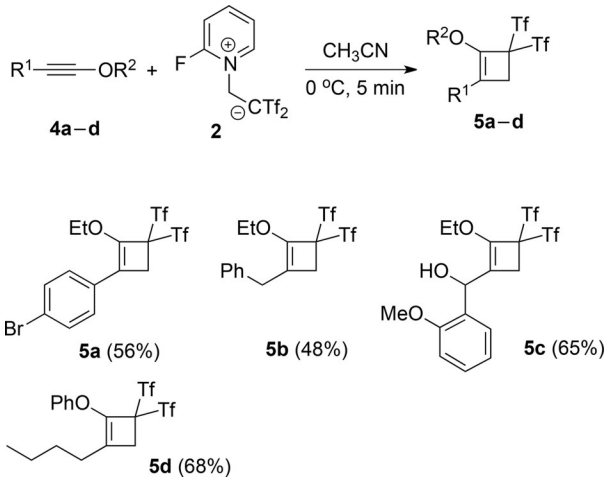


Figure 1. ORTEP drawing of bis(trifluoromethylsulfonyl)-bromocyclobutene **3d**. Thermal ellipsoids shown at 50% probability.

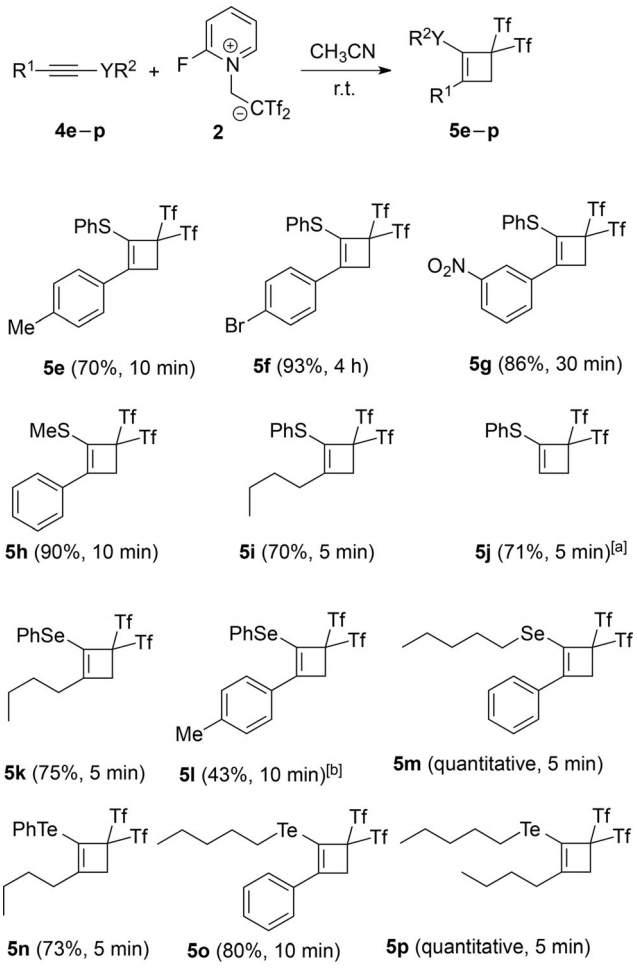
reasonable yields (Scheme 3). Remarkably, the presence of OR groups instead halogens at the starting alkyne reversed the product distribution completely, implying that the choice of substituents can control the regioselectivity of the reaction.



Scheme 3. Controlled preparation of bis(trifluoromethylsulfonyl)enol ether cyclobutenes **5a–d**.

Organosulfur compounds occupy a special position in heteroatom-containing small molecules, both as bioactive compounds as well as synthetic intermediates.[7] We envisaged the preparation of cyclobutene-triflones bearing S-based groups starting from thia-alkynes. The proposed thia-cyclobutene-triflones present intriguing structures, the stability of which was

initially in question given the supposed instability of chalcogen-substituted cyclobutene-triflones. Pleasingly, when using thia-alkynes **4e–j** and pyridinium salt **2**, thia-cyclobutene-triflones **5e–j** were isolated in high yields (Scheme 4), indicating the feasibility of this type of structures. In the case of sulfur-based substrates, the same level and sense of regioselectivity as in the oxygen derivatives was observed.

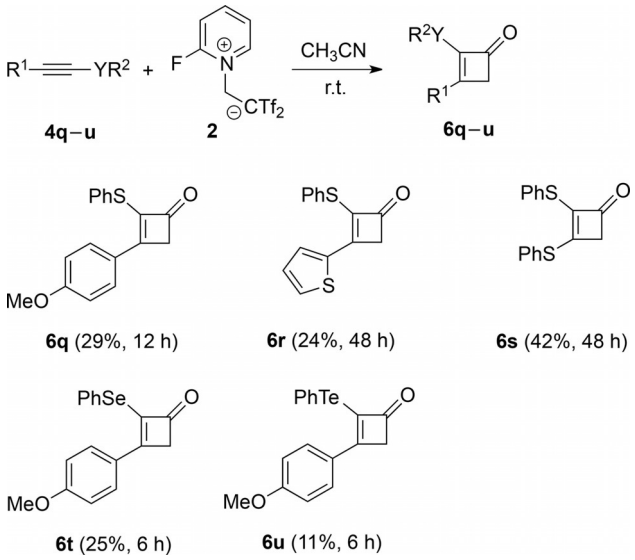


[a] The reaction was carried out at 0 °C.
[b] Partial decomposition during chromatographic purification.

Scheme 4. Controlled preparation of bis(trifluoromethylsulfonyl)chalcogen cyclobutenes **5**.

Cyclization precursors **4k–p** bearing Se- and Te-containing carbon chains were prepared. The standard cyclobutene formation conditions were then applied across this range of substrates. Alkynes **4k–p** efficiently formed the desired polyfunctionalized four-membered rings **5k–p**,[8] but the cyclization proved capricious for Se derivative **5l** due to partial degradation of the final material under the chromatographic purification conditions (Scheme 4). Interestingly, in all cases the product exhibited the same regiocontrol as the oxygen and sulfur derivatives.

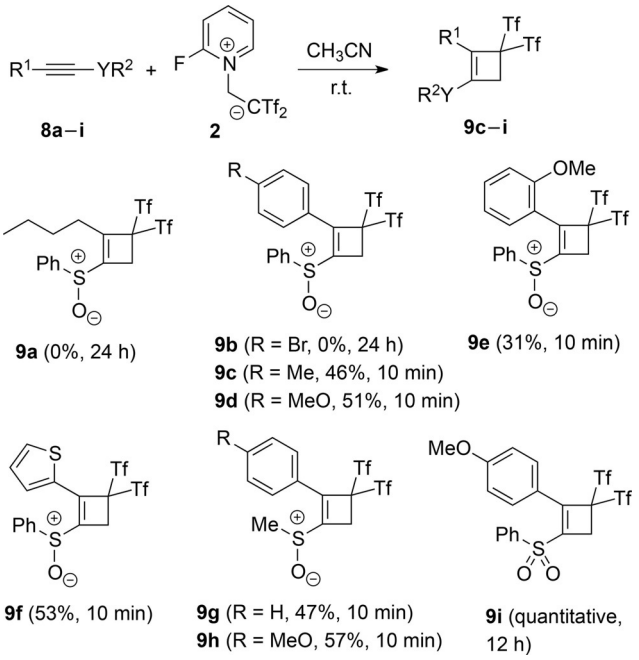
Chalcogen substrates **4q–u**, containing an additional electron-rich substituent at the other alkyne side, worked under the standard conditions to afford unexpected cyclobutene derivatives along with unidentified by-products. Cyclobutenones **6q–u** can be accessed from this type of substrates albeit with a lower yield (Scheme 5).



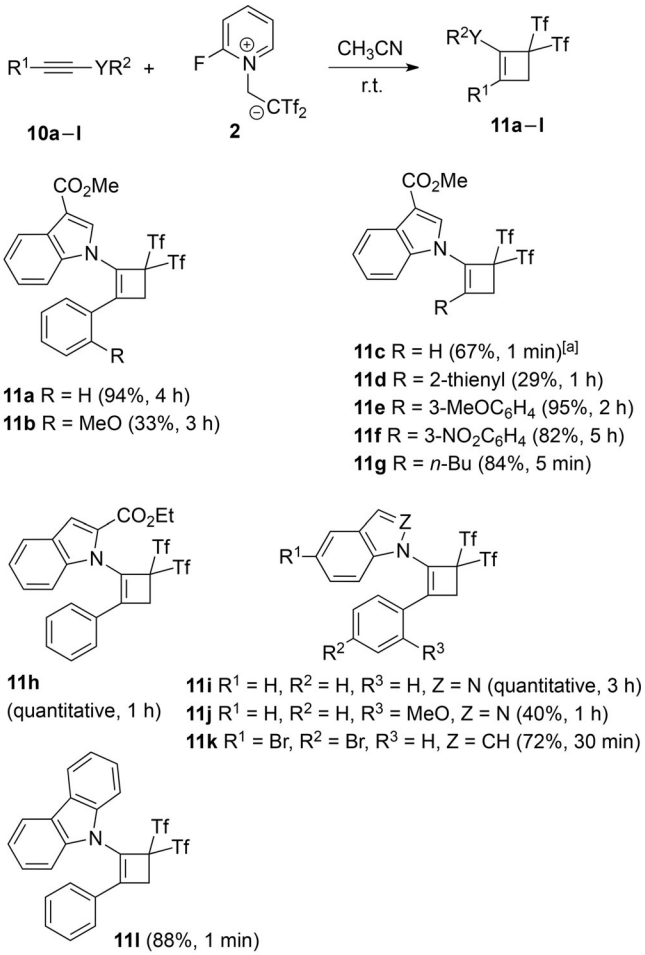
Scheme 5. Preparation of bis(trifluoromethylsulfonyl)chalcogen cyclobutenones **6**.

The influence of different sulfur oxidation states on the reactivity was also tested. In addition to thia-alkynes **4e–j** we were interested in examining sulfinylalkynes **8a–h** and sulfonylalkyne **8i**. Firstly, the electronic effect on the S-substituent was investigated and the result showed that substrates bearing aliphatic substituents (**8a**) or deactivated benzene rings (**8b**) did not afford the desired cyclobutenes. By contrast, neutral or electron-rich aromatic substituents can be tolerated to provide sulfinylcyclobutenes **9c–h** and sulfonylcyclobutene **9i** (Scheme 6). Notably, a regiochemistry reversal was observed on going from sulfur with oxidation number −2 such as in alkynes **4e–j** to sulfur with oxidation numbers +4 (alkynes **8c–h**) and +6 (alkyne **8i**).

The effect of an amino group in the four-membered ring formation reaction was investigated with the use of indole-based ynamine derivatives **10a–l**. As in the case of OR, SR, SeR, and TeR substituents (Scheme 3–Scheme 5), the regioselectivity reversal is dictated by the heteroatom. Ynamines **10a–l** afforded the corresponding cyclobutenes **11a–l** as the sole products in fair yields (Scheme 7). These examples also indicated that ynamines **11a**, **11h**, and **11i** bearing the simple phenyl ring at N-1 are the best starting materials, furnishing the highest yields (quantitative or almost quantitative yields) of the appropriate cyclo-



Scheme 6. Controlled preparation of bis(trifluoromethylsulfonyl)sulfinylcyclobutenes **9d–h** and sulfonylcyclobutene **9i**.



[a] The reaction was carried out at 0 °C.

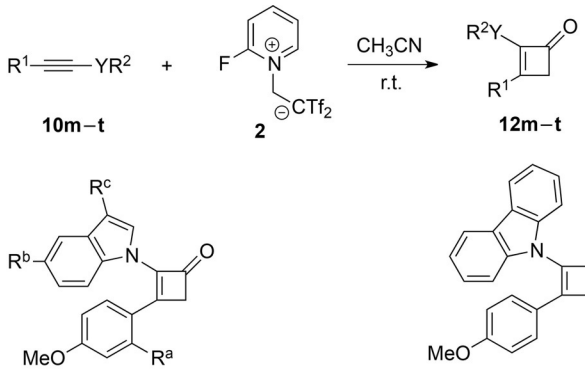
Scheme 7. Controlled preparation of bis(trifluoromethylsulfonyl)indolylcyclobutenes **11a–l**.

butenes. Unexpectedly, the results in Scheme 8 show, in all instances, that ynamines **10m–t** having electron-rich 4-$MeOC_6H_4$ groups furnished exclusively cyclobutenones **12m–t**.[9,10] Cyclobutenone formation is spontaneous under the reaction conditions, but it may be facilitated by the addition of water (2 equiv.) and K_2CO_3 (2 equiv.) during the work-up.

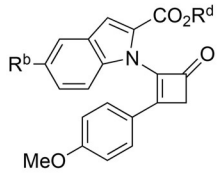
As shown in Scheme 9, the mechanism for the cyclobutenone formation involves two main processes, namely, cyclobutene ring construction and hydrolysis. The proposal for the first process (formation of **11m–t**) is based on our previous DFT studies of 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes,[5] but now the regioselectivity is dictated by the electronic effects of the heterocyclic amine. Adventitious water in the reaction medium is required for the double trifluoro(hydrosulfonyl)methane (TfH) elimination, giving rise to hydrates **17**. This two-fold water addition is assisted by the resonance effect of the 4-methoxy substituent in the 4-methoxyphenyl group. Finally, dehydration occurs in adducts **17** to afford cyclobutenones **12m–t**.

We decided to examine phosphorus-substituted alkynes **18** as precursors of functionalized cyclobutenes (Scheme 10).[11] Screening of precursors **18** revealed that phosphine oxides **18a** and **18b** afforded phosphorylcyclobutenes **19a** and **19b** in excellent yields under the usual mild conditions. However, despite the fact that apparently thiophosphine oxide **18c** is a suitable substrate for the reaction, it produced the S=$P(Ph)_2$-substituted cyclobutene **19c** in just 15% yield.

Taking into account the rich chemistry of organosilicon and organotin derivatives, we also became interested in the cyclobutenylation of trialkyl(ethynyl)silanes and trialkyl(ethynyl)stannanes by pyridinium salt **2** as cyclization reagent. If successful, this reaction could afford carbon(sp^2)-linked trialkylsilyl- and trialkylstannylcyclobutenes. The formation of the expected TMS-cyclobutene **21a** was observed by TLC, but it could not be isolated for synthetic purposes. We were pleased to observe that the reaction of the TIPS-alkyne **20b** afforded the corresponding TIPS-cyclobutene **21b** in high yield (Scheme 11). An unexpected product was obtained starting from Bu_3Sn-alkyne **22a**, the identity of which was assigned as **23a** and resulted from the transformation of the Bu_3Sn group rather than the alkyne moiety. A similar behaviour was detected in the conversion of organotin derivative **22b** into adduct **23b**. Interestingly, stirring alkynylstannane **22c** at room temperature in acetonitrile with zwitterion **2** led to the formation of tetra(trifluoromethylsulfonyl)cyclobutene **24c**, in 61% isolated yield in just 10 min (Scheme 11). Noticeably, compounds **23a**, **23b**,



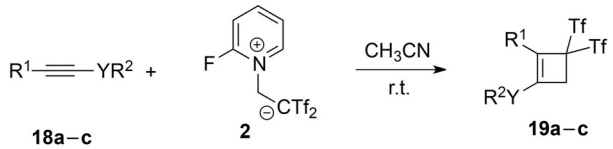
12m R^a = H, R^b = H, R^c = CO_2Me (86%, 12 h) **12p** (88%, 12 h)
12n R^a = MeO, R^b = H, R^c = CO_2Me (23%, 12 h)[a]
12o R^a = H, R^b = Br, R^c = H (42%, 12 h)

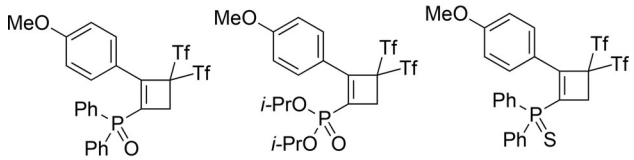


12q R^b = H, R^d = Et (53%, 12 h)
12r R^b = Me, R^d = Et (45%, 12 h)
12s R^b = Cl, R^d = Et (51%, 12 h)
12t R^b = H, R^d = Ph (41%, 72 h)

[a] Messy reaction.

Scheme 8. Controlled preparation of bis(trifluoromethylsulfonyl)indolylcyclobutenones **12m–t**.



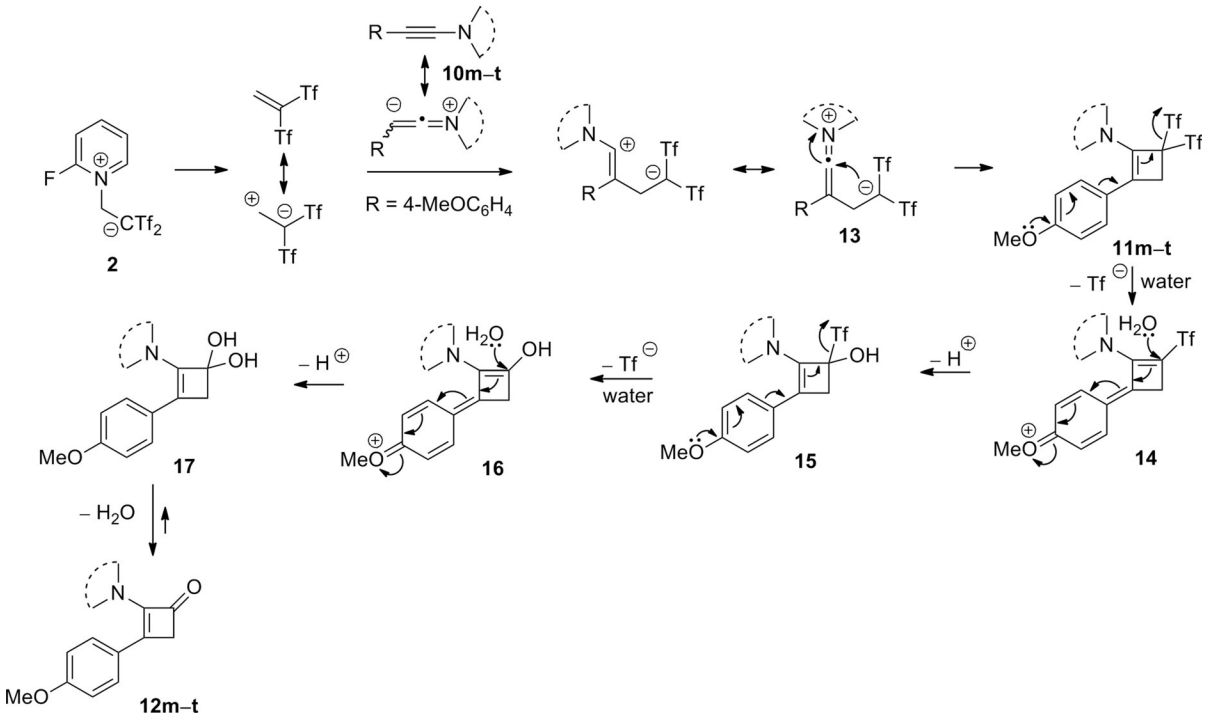


19a (89%, 12 h) **19b** (94%, 6 h) **19c** (15%, 12 h)

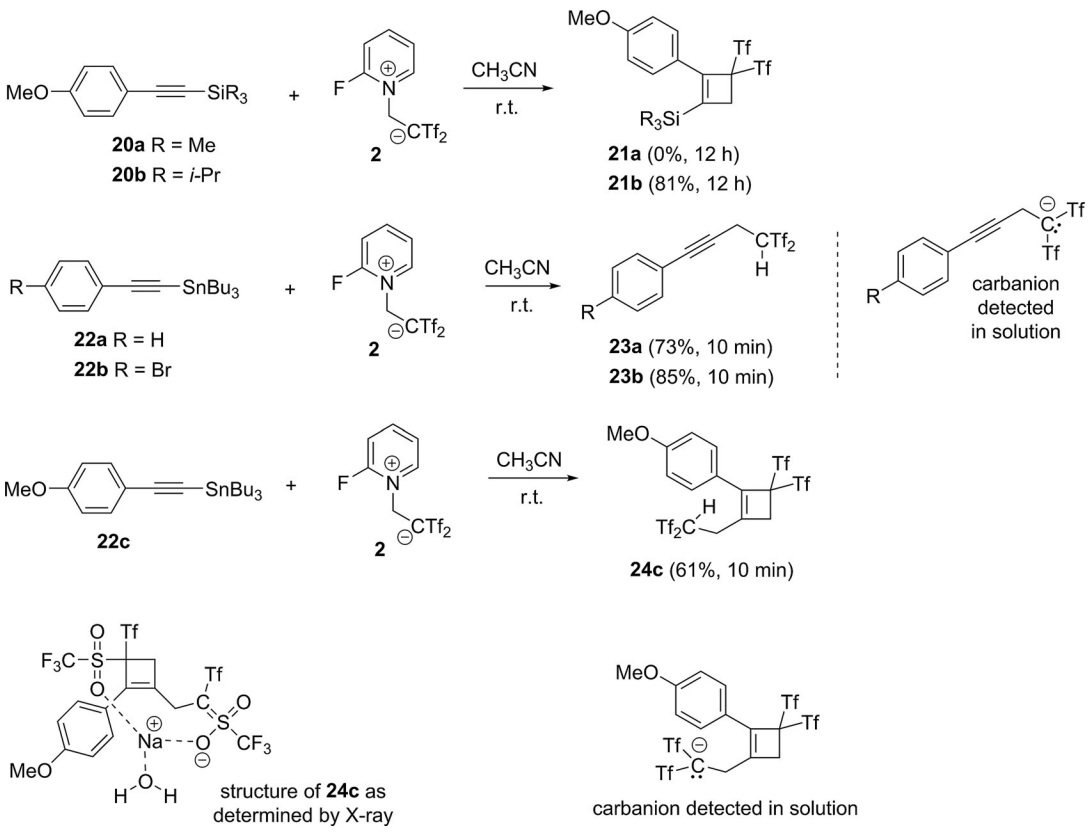
Scheme 10. Controlled preparation of bis(trifluoromethylsulfonyl)phosphorylcyclobutenes **19a–c**.

and **24c** are carbon acids which in solution easily dissociate the acidic hydrogen and give rise to stable carbanions.[12] When the ^{1}H NMR spectra of **23a**, **23b**, and **24c** were reorded, the signals for the hydrogen atoms of the Tf_2CH group could not be detected. Further supporting structural evidence was obtained through the X-ray crystallographic analysis of adduct **24c** (Figure 2).[13]

To evaluate the goal of chemoselectivity, several functionalized heteroatom-containing alkynes **25a–c** were reacted under the above standard reaction conditions. Every single reaction reached full conversion to selectively afford cyclobutenes **26a–c**, in which monocyclization towards the heteroatom-substituted alkyne was favoured. Bis-functionalization of the remaining alkyne or azide functionality was achieved after the addition of a second equivalent of zwitterion **2**, suggesting that the exquisite selectivity arises from the increased reactivity imparted by the heteroatom (Scheme 12).



Scheme 9. Rationalization for the formation of cyclobutenones **12**.



Scheme 11. Controlled preparation of bis(trifluoromethylsulfonyl)silacyclobutene **21b** and triflone carbanions **23a**, **23b** and **24c**.

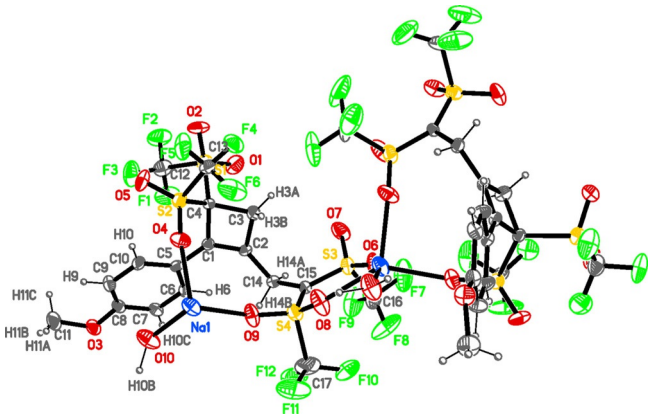


Figure 2. ORTEP drawing of tetra(trifluoromethylsulfonyl)-cyclobutene **24c**. Thermal ellipsoids shown at 50% probability.

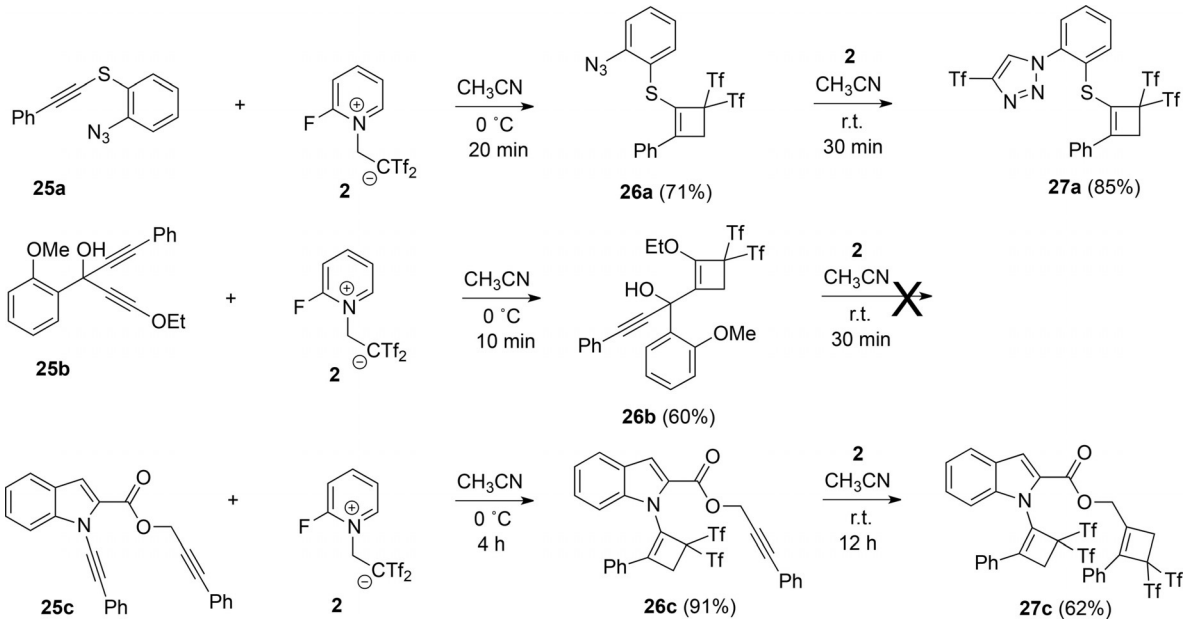
Conclusions

In summary, we have developed a new metal-free synthesis of a vast variety of heteroatom-containing cyclobutene-triflones and cyclobutenones from the reaction of heteroatom-substituted alkynes with a pyridinium salt as a $Tf_2C{=}CH_2$ source. This powerful methodology, involving cyclization, allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulfur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S instruments. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), acetone-d_6 (^{1}H, 2.05 ppm; ^{13}C, 206.3 ppm), C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm), or DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Low and high resolution mass spectra were taken on an Agilent 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation ($\lambda =$ 0.71073 Å) operating at 50 kV and 35 mA with an exposure of 30.18 s in ω. All commercially available compounds were used without further purification.



Scheme 12. Chemoselective reaction of heteroatom-containing alkynes **25**.

General Procedure for the Reaction of Heteroatom-Substituted Alkynes and Pyridinium Salt 2

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (0.2 mmol) was added at room temperature (or 0 °C) to a solution of the appropriate heteroatom-substituted alkyne **1a–f**, **4a–u**, **8a–i**, **10a–l**, **18a–c**, **20a**, **20b**, **22a–c**, **25a–c**, or **26a–c** (0.2 mmol) in acetonitrile (4 mL). The reaction mixturewas stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **3a–f**, **5a–p**, **6q–u, 9c–i**, **11a–l**, **19a–c**, **21b**, **23a**, **23b**, **24c**, **26a–c**, **271**, **and 27c** are given in the following paragraphs.[14]

Bis(trifluoromethylsulfonyl)iodocyclobutene (3c): From 43 mg (0.16 mmol) of alkyne **1c**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3c** as a pale yellow solid; yield: 153 mg (97%); mp 83–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.91 (m, 2H, 2 CH^{Ar}), 6.98 (m, 2H, 2 CH^{Ar}), 3.86 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.5 ($C^{Ar\text{-}q}$–OCH_3), 142.4 (*C*=C–I), 128.7 (2 CH^{Ar}), 121.2 ($C^{Ar\text{-}q}$), 119.7 (q, $J_{C,F}$ = 331.5 Hz, 2 CF_3), 114.1 (2 CH^{Ar}), 93.7 (C=*C*–I), 90.0 (CTf_2), 55.4 (CH_3O), 42.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.61 (s, 6F, 2 CF_3); IR ($CHCl_3$): ν = 1608 (C=C), 1384, 1103 (O=S=O), 1207 cm^{-1} (C–F); HR-MS (ES): *m/z* = 567.9177, calcd. for $C_{13}H_{13}IF_6NO_5S_2$ $[M+NH_4]^+$: 567.9179.

Bis(trifluoromethylsulfonyl)phenoxycyclobutene (5d): From 20 mg (0.11 mmol) of alkyne **4d**, and after flash chromatography of the residue using hexanes/toluene (9:1→8:2) as eluent gave compound **5d** as a colourless oil; yield: 36 mg (68%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 2H, 2 CH^{Ar}), 7.22 (m, 3H, 3 CH^{Ar}), 2.98 (s, 2H, CH_2-*cyclobutenyl*), 1.77 (t, 3H, *J* = 7.2 Hz, CH_2), 1.24 (m, 4H, 2 CH_2), 0.79 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.1 ($C^{Ar\text{-}q}$–O), 133.7 (C=*C*–O), 132.5 (*C*=C–O), 129.9 (2 CH^{Ar}), 125.6 (CH^{Ar}), 119.7 (q, $J_{C,F}$ = 330.5 Hz, 21 CF_3), 119.0 (2 CH^{Ar}), 86.8 (CTf_2), 30.0 (CH_2-*cyclobutenyl*), 27.8 (CH_2), 27.0 (CH_2), 22.1 (CH_2), 13.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.91 (s, 6F, 2 CF_3); IR ($CHCl_3$): ν = 1695 (C=C), 1383, 1106 (O=S=O), 1204 cm^{-1} (C–F); HR-MS (ES): *m/z* = 484.0671, calcd. for $C_{16}H_{20}F_6NO_5S_2$ $[M+NH_4]^+$: 484.0682.

Bis(trifluoromethylsulfonyl)thiocyclobutene (5f): From 30 mg (0.103 mmol) of alkyne **4f**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **5f** as a colourless oil; yield: 56 mg (93%). ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.25 (m, 2H, 2 CH^{Ar}), 6.96 (m, 2H, 2 CH^{Ar}), 6.79 (m, 5H, 5 CH^{Ar}), 3.17 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 159.0 (C=*C*–S), 131.9 (2 CH^{Ar}), 130.3 ($C^{Ar\text{-}q}$), 129.7 (2 CH^{Ar}), 129.6 (2 CH^{Ar}), 129.5 (2 CH^{Ar}), 128.6 ($C^{Ar\text{-}q}$), 128.0 (CH^{Ar}), 126.9 ($C^{Ar\text{-}q}$), 120.3 (q, $J_{C,F}$ = 331.1 Hz, 2 CF_3), 121.0 (*C*=C–S), 89.2 (CTf_2), 34.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −70.29 (s, 6F, 2 CF_3); IR (CH_2Cl_2): ν = 1599 (C=C), 1383, 1106 (O=S=O), 1207 cm^{-1} (C–F); HR-MS (ES): *m/z* = 597.9231, calcd. for $C_{18}H_{15}BrF_6NO_4S_3$ $[M+NH_4]^+$: 597.9245.

Bis(trifluoromethylsulfonyl)selenocyclobutene (5m): From 30 mg (0.12 mmol) of alkyne **4m**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (95:5) as eluent gave compound **5m** as a colourless oil; yield: 64 mg (quantitative). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (m, 2H, 2 CH^{Ar}), 7.51 (m, 3H, 3 CH^{Ar}), 3.76 (s, 2H, CH_2-*cyclobutenyl*), 3.04 (t, 2H, *J* = 7.5 Hz, CH_2), 1.73 (m, 2H, CH_2), 1.33 (m, 4H, 2 CH_2), 0.86 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.6 (*C*=C–Se), 131.9 (CH^{Ar}), 130.7 ($C^{Ar\text{-}q}$), 128.9 (2 CH^{Ar}), 127.4 (2 CH^{Ar}), 119.8 (q, $J_{C,F}$ = 331.3 Hz, 2 CF_3), 115.0 (C=*C*–Se), 87.8 (CTf_2), 36.4 (CH_2-*cyclobutenyl*), 31.7 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 22.0 (CH_2), 13.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.23 (s, 6F, 2 CF_3); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 245.0 (s, 1Se, Se); IR ($CHCl_3$): ν = 1381,

1106 (O=S=O), 1203 cm^{-1} (C–F); HR-MS (ES): m/z = 562.0037, calcd. for $C_{17}H_{22}F_6NO_4S_2Se$ $[M+NH_4]^+$: 562.0054.

Bis(trifluoromethylsulfonyl)tellurocyclobutene (5p): From 50 mg (0.178 mmol) of alkyne **4p**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **5p** as a pale yellow oil; yield: 102 mg (quantitative). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.62 (s, 2H, CH_2-*cyclobutenyl*), 2.90 (t, 2H, J = 7.6 Hz, CH_2), 2.43 (t, 2H, J = 7.4 Hz, CH_2), 1.82 (m, 2H, CH_2), 1.41 (m, 8H, 4CH_2), 0.91 (m, 6H, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 178.6 (*C*=C-Te), 119.9 (q, J_{CF} = 331.1 Hz, 2CF_3), 98.3 (C=*C*-Te), 86.5 (CTf_2), 39.8 (CH_2-*cyclobutenyl*), 33.9 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 13.9 (CH_3), 13.7 (CH_3), 10.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.27 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1605 (C=C), 1380, 1107 (O=S=O), 1203 cm^{-1} (C–F); HR-MS (ES): m/z = 592.0254, calcd. for $C_{15}H_{26}F_6O_4S_2Te$ $[M+NH_4]^+$: 592.0260.

Thiocyclobutenone (6s): From 30 mg (0.12 mmol) of alkyne **4s**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6s** as a pale yellow oil; yield: 15 mg (42%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37 (m, 10H, 10CH^{Ar}), 3.31 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 182.0 (C=O), 172.9 (*C*=C), 134.1 (2CH^{Ar}), 131.6 ($C^{Ar\text{-}q}$), 130.4 (2CH^{Ar}), 130.1 (CH^{Ar}), 129.6 ($C^{Ar\text{-}q}$), 129.4 (2CH^{Ar}), 129.0 (2CH^{Ar}), 128.4 (C=*C*), 127.2 (CH^{Ar}), 52.3 (CH_2); IR ($CHCl_3$): ν = 1742 cm^{-1} (C=O); HR-MS (ES): m/z = 285.0410, calcd. for $C_{16}H_{13}OS_2$ $[M+H]^+$: 285.0402.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene (9f): From 15 mg (0.064 mmol) of alkyne **8f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound **9f** as a pale yellow oil; yield: 18 mg (53%). ^{1}H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.92 (d, 1H, J = 3.1 Hz, CH^{Ar}), 7.53 (m, 2H, 2CH^{Ar}), 6.95 (m, 3H, 3CH^{Ar}), 6.67 (d, 1H, J = 5.0 Hz, CH^{Ar}), 6.38 (t, 1H, J = 4.4 Hz, CH^{Ar}), 3.53 (d, 1H, J = 15.7 Hz, CH*H*-*cyclobutenyl*), 2.93 (d, 1H, J = 15.7 Hz, C*H*H-*cyclobutenyl*); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ = 146.0 (C=*C*–S), 141.0 ($C^{Ar\text{-}q}$), 134.1 (CH^{Ar}), 132.3 (*C*=C–S), 132.2 (CH^{Ar}), 131.9 (CH^{Ar}), 129.7 (2CH^{Ar}), 128.7 (CH^{Ar}), 127.6 ($C^{Ar\text{-}q}$), 124.1 (2CH^{Ar}), 120.2 (q, $J_{C,F}$ = 331.8 Hz, CF_3), 119.9 (q, $J_{C,F}$ = 331.6 Hz, CF_3), 84.4 (CTf_2), 33.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −70.74 (s, 3F, CF_3), −71.63 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1386, 1105 (O=S=O), 1212 cm^{-1} (C–F); HR-MS (ES): m/z = 524.9400, calcd. for $C_{16}H_{11}F_6O_5S_4$ $[M+H]^+$: 524.9388.

Bis(trifluoromethylsulfonyl)sulfonylcyclobutene (9i): From 44 mg (0.16 mmol) of alkyne **8i**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **9i** as a colourless solid; yield: 90 mg (quantitative); mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.07 (m, 2H, 2CH^{Ar}), 7.93 (m, 2H, 2CH^{Ar}), 7.71 (m, 1H, CH^{Ar}), 7.59 (m, 2H, 2CH^{Ar}), 6.97 (m, 2H, 2CH^{Ar}), 3.88 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.0 ($C^{Ar\text{-}q}$–OCH_3), 141.9 (*C*=C–SO_2Ph), 139.1 (C=*C*–SO_2Ph), 137.5 ($C^{Ar\text{-}q}$), 135.0 (CH^{Ar}), 132.5 (2CH^{Ar}), 129.7 (2CH^{Ar}), 127.9 (2CH^{Ar}), 119.6 (q, $J_{C,F}$ = 331.5 Hz, 2CF_3), 119.5 ($C^{Ar\text{-}q}$), 114.3 (2CH^{Ar}), 84.2 (CTf_2), 55.5 (OCH_3), 35.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.51 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1599 (C=C), 1386, 1101 (O=S=O>), 1212 cm^{-1} (C–F); HR-MS (ES): m/z = 582.0155, calcd. for $C_{19}H_{18}F_6NO_7S_3$ $[M+NH_4]^+$: 582.0144.

Bis(trifluoromethylsulfonyl)aminocyclobutene (11a): From 20 mg (0.07 mmol) of alkyne **10a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **11a** as a colourless solid; yield: 38 mg (94%); mp 117–119 °C. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 8.65 (d, 1H, J = 8.0 Hz, CH^{Ar}), 8.35 (s, 1H, NCH^{Ar}), 7.40 (d, 1H, J = 8.3 Hz, CH^{Ar}), 7.15 (m, 1H, CH^{Ar}), 6.98 (m, 1H, CH^{Ar}), 6.84 (m, 1H, CH^{Ar}), 6.65 (m, 4H, 4CH^{Ar}), 3.48 (s, 3H, CH_3), 3.11 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 164.0 (C=O), 152.9 (C=*C*–N), 136.4 (*C*=C–N), 132.5 (CH^{Ar}), 131.7 (CH^{Ar}), 129.1 (2CH^{Ar}), 128.4 (2CH^{Ar}), 128.2 ($C^{Ar\text{-}q}$), 126.9 ($C^{Ar\text{-}q}$), 125.0 (CH^{Ar}), 124.0 (CH^{Ar}), 123.0 (CH^{Ar}), 120.1 (q, $J_{C,F}$ = 330.8 Hz, 2CF_3), 118.9 ($C^{Ar\text{-}q}$), 112.8 ($C^{Ar\text{-}qo}$), 112.0 (CH^{Ar}), 90.0 (CTf_2), 51.0 (CH_3), 31.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −70.44 (s, 6F, 2CF_3); IR (CH_2Cl_2): ν = 1711 (C=O), 1375, 1102 (O=S=O), 1196 cm^{-1} (C–F); HR-MS (ES): m/z = 585.0559, calcd. for $C_{22}H_{19}F_6N_2O_6S_2$ $[M+NH_4]^+$: 585.0583.

Bis(trifluoromethylsulfonyl)phosphinylcyclobutene (19b): From 53 mg (0.18 mmol) of alkyne **18b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **19b** as a colouirless oil; yield: 99 mg (94%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (m, 2H, 2CH^{Ar}), 6.95 (m, 2H, 2CH^{Ar}), 4.76 (m, 2H, 2CH), 3.85 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2), 1.37 (d, 6H, J = 6.2 Hz, 2CH_3), 1.27 (d, 6H, J = 6.2 Hz, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.1 ($C^{Ar\text{-}q}$–OCH_3), 145.6 (d, $J_{C,P}$ = 9.9 Hz, *C*=C–P), 136.6 (d, $J_{C,P}$ = 188.7 Hz, C=*C*-,P), 131.1 (2CH^{Ar}), 121.5 ($C^{Ar\text{-}q}$), 119.8 (q, $J_{C,F}$ = 331.6 Hz, 2CF_3), 114.0 (2CH^{Ar}), 86.3 (d, $J_{C,P}$ = 35.8 Hz, CTf_2), 72.5 (d, $J_{C,P}$ = 5.6 Hz, 2CH), 55.3 (OCH_3), 36.0 (d, $J_{C,P}$ = 7.9 Hz, CH_2), 24.0 (d, $J_{C,P}$ = 4.1 Hz, 2CH_3), 23.7 (d, $J_{C,P}$ = 5.0 Hz, 2CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.57 (s, 6F, 2CF_3); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ = 4.48 [s, P, P=O(O-*i*-Pr)$_2$]; IR ($CHCl_3$): ν = 1605 (C=C), 1387, 1103 (O=S=O), 1206 (C–F), 988 cm^{-1} (P=O); HR-MS (ES): m/z = 611.0353 calcd. for $C_{19}H_{23}F_6O_8PS_2Na$ $[M+Na]^+$: 611.0368.

Bis(trifluoromethylsulfonyl)silacyclobutene (21b): From 50 mg (0.17 mmol) of alkyne **20b**, and after flash chromatography of the residue using hexanes/ethyl acetate (99:1) as eluent gave compound **21b** as a colourless oil; yield: 80 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (m, 2H, 2CH^{Ar}), 6.89 (m, 2H, 2CH^{Ar}), 3.84 (s, 3H, OCH_3), 3.32 (s, 2H, CH_2), 1.10 (m, 21H, 3CH+6CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.3 (*C*=C–Si), 160.7 ($C^{Ar\text{-}q}$–OCH_3), 149.0 (C=*C*–Si), 129.9 (2CH^{Ar}), 125.1 ($C^{Ar\text{-}q}$), 119.8 (q, $J_{C,F}$ = 331.1 Hz, 2CF_3), 113.5 (2CH^{Ar}), 90.1 (CTf_2), 55.2 (OCH_3), 36.2 (CH_2), 18.4 (6CH_3), 11.5 (3CH); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −70.29 (s, 6F, 2CF_3); IR ($CHCl_3$): ν = 1614 (C=C), 1379, 1106 (O=S=O), 1203 cm^{-1} (C–F); HR-MS (ES): m/z = 598.1566, calcd. for $C_{22}H_{31}F_6NO_5S_2Si$ $[M+NH_4]^+$: 598.1546.

Bis(trifluoromethylsulfonyl)bis(trifluoromethylsulfonyl)-cyclobutene (24c): From 20 mg (0.047 mmol) of alkyne **22c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **24c** as a colourless solid; yield: 21 mg (61%); mp 153–155 °C- ^{1}H NMR (300 MHz, acetone-d_6, 25 °C): δ = 7.60 (m, 2H, 2CH^{Ar}), 6.96 (m, 2H, 2
CH^{Ar}), 3.80 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 3.51 (s, 2H,

CH_2-*cyclobutenyl*) – the signal of $CHTf_2$ is not visible in the ^{1}H NMR spectrum because of its acidity; ^{13}C NMR (75 MHz, acetone-d_6, 25 °C): $\delta = 161.3$ ($C^{Ar\text{-}q}$–OCH_3), 156.4 (*C*=*C*), 130.5 (C=*C*), 130.2 (2 CH^{Ar}), 123.5 ($C^{Ar\text{-}q}$), 122.6 (q, $J_{C,F} = 327.7$ Hz, 2 CF_3), 120.9 (q, $J_{C,F} = 331.1$ Hz, 2 CF_3-*cyclobutenyl*), 114.9 (2 CH^{Ar}), 86.9 (CTf_2-*cyclobutenyl*), 61.2 (CTf_2), 55.8 (OCH_3), 37.5 (CH_2-*cyclobutenyl*), 29.6 (CH_2) – the signal of $CHTf_2$ is visible in the ^{13}C NMR spectrum as a quaternary carbon rather than as a CH because of the deprotonation; ^{19}F NMR (282 MHz, acetone-d_0, 25 °C): $\delta = -72.04$ (s, 6 F, 2 CF_3-*cyclobutenyl*), −80.10 (s, 6 F, 2 CF_3); IR (acetone): $\nu = 1608$ (C=C), 1380, 1099 (O=S=O), 1346, 1042 (O=S=O), 1192 cm^{-1} (C–F); HR-MS (ES): $m/z = 733.9513$ calcd. for $C_{17}H_{16}F_{12}NO_9S_4$ $[M+NH_4]^+$: 733.9511.

Bis(trifluoromethylsulfonyl)thiocyclobutene (27a): From 15 mg (0.027 mmol) of azide **26a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **27a** as a yellow oil; yield: 17 mg (85%). ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): $\delta = 8.80$ (s, 1 H, CH-*triazolyl*), 7.87 (m, 2 H, 2 CH^{Ar}), 7.76 (m, 1 H, CH^{Ar}), 7.63 (m, 1 H, CH^{Ar}), 7.54 (m, 4 H, 4 CH^{Ar}), 7.49 (m, 1 H, CH^{Ar}), 3.68 (s, 2 H, CH_2); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): $\delta = 165.9$ (C=*C*–S), 139.5 ($C^{Ar\text{-}q}$–Tf), 136.1 (*C*=C–S), 134.5 (CH^{Ar}), 133.7 (CH^{Ar}), 133.1 (CH^{Ar}), 131.8 (CH^{Ar}), 130.1 (CH^{Ar}), 129.5 (2 CH^{Ar}), 129.3 ($C^{Ar\text{-}q}$), 128.1 (2 CH^{Ar}), 127.4 ($C^{Ar\text{-}q}$), 127.1 (CH^{Ar}), 119.6 (q, $J_{C,F} = 330.8$ Hz, 2 CF_3), 119.4 (q, $J_{C,F} = 324.4$ Hz, CF_3), 116.7 ($C^{Ar\text{-}q}$), 88.0 (CTf_2), 35.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta = -70.44$ (s, 6 F, 2 CF_3), −78.50 (s, 3 F, CF_3); IR ($CHCl_3$): $\nu = 1385$, 1104 (O=S=O), 1214 cm^{-1} (C–F); HR-MS (ES): $m/z = 718.9797$ calcd. for $C_{21}H_{16}F_9N_4O_6S_4$ $[M+NH_4]^+$: 718.9803.

General Procedure for the Uncatalyzed Reaction of Heteroatom-Substituted Alkynes 10m–t and Pyridinium Salt 2. Synthesis of Cyclobutenones 12m–t

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide 2 (0.2 mmol) was added at room temperature to a solution of the appropriate ynamine **10m–t** (0.2 mmol) in acetonitrile (4 mL). The reaction mixture was stirred at room temperature until disappearance of the starting material (TLC). Saturated potassium carbonate (2 mL) was added and the mixture was stirred for 10 min, before being partitioned between ethyl acetate and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for one example of adducts **12m–t** are given below.

Aminocyclobutenone (12p): From 20 mg (0.07 mmol) of alkyne **10p**, and after flash chromatography of the residue using hexanes/ethyl acetate (85:15) as eluent gave compound **12p** as a colourless solid; yield: 20 mg (88%); mp 154–156 °C. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): $\delta = 7.96$ (d, 2 H, $J = 7.7$ Hz, 2 CH^{Ar}), 7.41 (d, 2 H, $J = 8.0$ Hz, 2 CH^{Ar}), 7.28 (m, 2 H, 2 CH^{Ar}), 7.21 (m, 2 H, 2 CH^{Ar}), 6.95 (m, 2 H, 2 CH^{Ar}), 6.38 (m, 2 H, 2 CH^{Ar}), 3.11 (s, 2 H, CH_2). 3.07 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): $\delta = 183.8$ (C=O), 162.5 ($C^{Ar\text{-}q}$–OCH_3), 157.7 (C=*C*–N), 139.0 (2 $C^{Ar\text{-}q}$), 132.9 (2 CH^{Ar}), 128.7 (*C*=C--N), 126.5 (2 CH^{Ar}), 124.5 (2 $C^{Ar\text{-}q}$), 123.9 ($C^{Ar\text{-}q}$), 121.3 (2 CH^{Ar}), 120.7 (2 CH^{Ar}), 114.3 (2 CH^{Ar}), 112.5 (2 CH^{Ar}), 54.8 (OCH_3), 45.5 (CH_2); IR (CH_2Cl_2): $\nu = 1760$ (C=O), 1602 (C=C), 1262 cm^{-1} (C–O); HR-MS (ES): $m/z = 340.1324$, calcd. for $C_{23}H_{18}NO$ $[M+H]^+$: 340.1332.

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Synthetic Methods |*Hot Paper*|

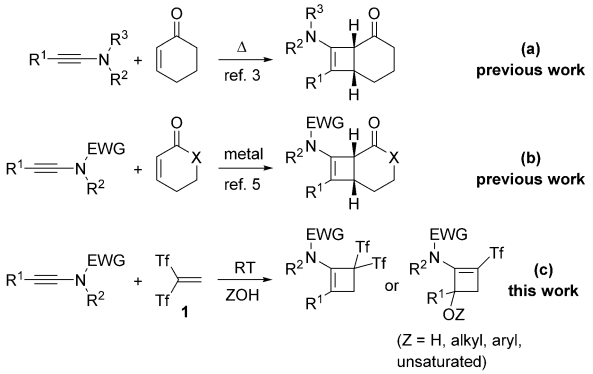
Direct Metal-Free Entry to Aminocyclobutenes or Aminocyclobutenols from Ynamides: Synthetic Applications

Benito Alcaide,*[a] Pedro Almendros,*[b] and Carlos Lázaro-Milla[a]

Abstract: The [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ has been developed to regioselectively afford bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with the ynamides bearing electron-rich aromatic rings at the C-terminal, an interesting reactivity switch was observed; a cyclization/hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. Aminocyclobutene construction with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3-(triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

Introduction

Functionalized cyclobutenes are important scaffolds present in several bioactive compounds, which have also been used as synthetic intermediates for the preparation of functionalized organic molecules.[1] Of particular interest is the aminocyclobutene structural motif.[2] A traditional method for aminocyclobutene preparation in a single step is the Ficini reaction, a [2+2] cycloaddition of ynamines with cyclic electron-deficient alkenes (Scheme 1 a).[3] However, the Ficini reaction presents a serious drawback, owing to the difficulty of preparing and handling reactive ynamines. More recently, ynamides,[4] which bear increased stability, has been proved as convenient substrates for the Ficini reaction (Scheme 1 b).[5] Unfortunately, their widespread use in aminocyclobutene synthesis is precluded by the narrow substrate scope of the alkene partner, which is normally a cyclic α,β-unsaturated carbonyl compound. An additional drawback is the use of environmentally unfriendly or expensive metallic salts, which are required for the activation of ynamides. Consequently, efficient metal-free synthesis of functionalized aminocyclobutenes with high chemo- and regioselectivity remains a challenge.



Scheme 1. [2+2] cycloadditions of ynamides with alkenes.

We contemplated a possible mild, metal-free synthesis of aminocyclobutenes through the reaction of the highly polarized reagent 1,1-bis(trifluoromethylsulfonyl)ethene (**1**)[6] with ynamides (Scheme 1 c). Of practical interest, 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** was identified as a stable precursor of **1** with the transference of the Tf_2CCH_2 group to phenols, alkynes, 1,3-dienes, and azides.[7] Herein we describe the discovery and development of the uncatalyzed [2+2] cycloaddition of ynamides with $Tf_2C{=}CH_2$ **1** under mild conditions. Incidentally, with ynamides bearing electron-rich aromatic rings at the C-terminal, we observed an interesting reactivity switch.

Results and Discussion

Figure 1 and Figure 2 show the structures of starting ynamides **3a–j** and **3k–z′**, respectively. Initially we treated the oxazolidi-

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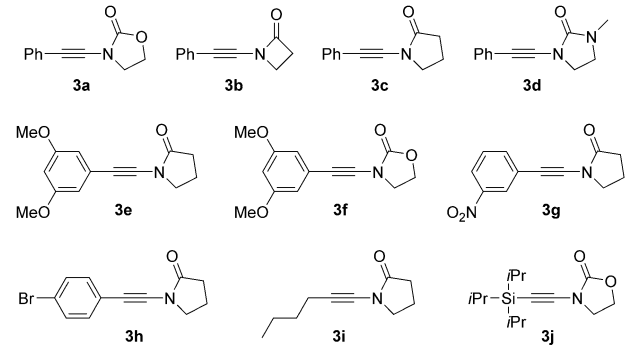


Figure 1. Structures of starting ynamides **3a–j**.

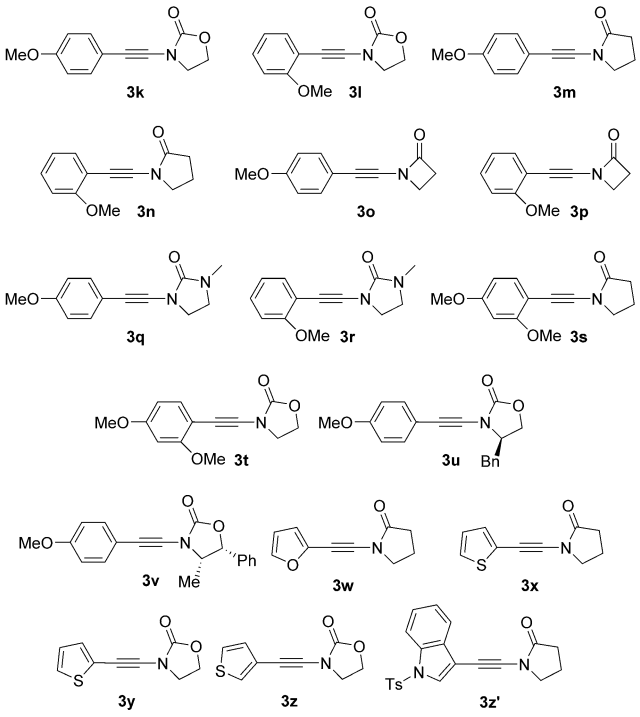
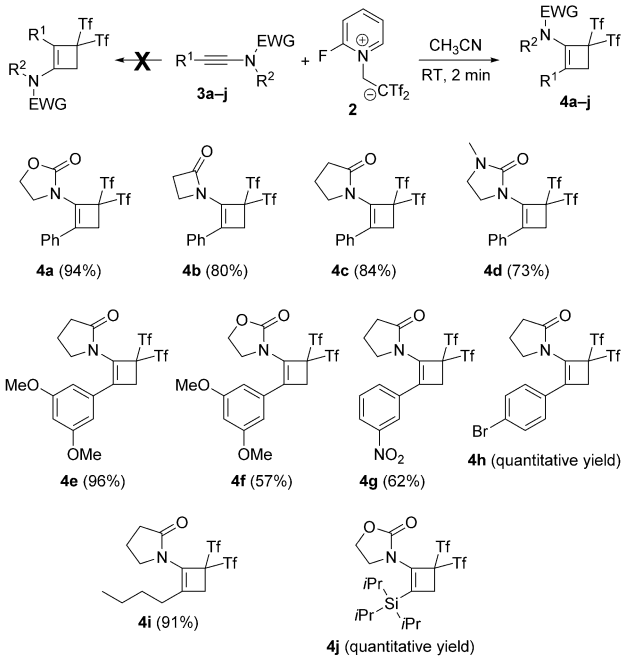


Figure 2. Structures of starting ynamides **3k–z′**.

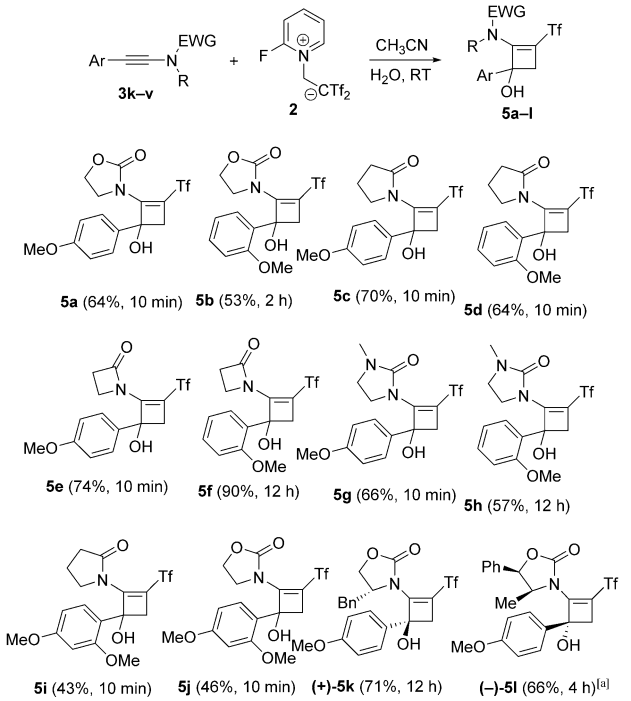
none-based phenyl ynamide **3a** with zwitterion **2** in acetonitrile at room temperature (the optimal conditions identified earlier in our laboratory for the reaction of pyridinium salt **2**).[7c,d] The nitrogenated functionality of ynamides can either become part of a possible five-membered azaheterocycle or be introduced as an amino substituent onto the required cyclobutene. Happily, the desired 4,4-bis(trifluoromethylsulfonyl)-cyclobut-1-enamide **4a** was cleanly formed with total regioselectivity and isolated in an excellent 94% yield (Scheme 2). It is important to note that excess of pyridinium salt **2** was not required and the use of equimolecular amounts of zwitterion was enough, thus not generating additional waste. Next, we decide to evaluate the generality of the reaction with respect to nitrogen functionalization. Azetidin-2-one-, pyrrolidin-2-one-, and imidazolidin-2-one-based phenyl ynamides **3b–d** were selected as the substrates to test our cyclization reaction. We



Scheme 2. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **4**.

were pleased to find that the desired four-membered carbocyclic products **4b–d** were smoothly obtained (Scheme 2). We then turned to examine a series of ynamides by varying substitution on the C-terminal. Thus, dimethoxyphenyl, nitrophenyl, and bromophenyl ynamides **3e–h** afforded adducts **4e–h** in 57%-quantitative yields (Scheme 2). The process was not limited to aromatic ynamides; alkyl-substituted ynamide **3i** also performed well to produce the expected product **4i**. Likewise, the silyl-protected acetylene **3j** survived the reaction very well to form **4j** in quantitative yield (Scheme 2). Ynamides that contained substituents with different electronic features were well-tolerated; with the present method becoming a facile route to aminocyclobutene scaffolds. Notably, ynamides **3a–j** instantaneously reacted to selectively give the corresponding aminocyclobutenes **4a–j**.[8]

Next, the general scope of the reaction with ynamides that contained electron-donating methoxy groups at the *ortho* or *para* positions of the benzene ring was examined. When electron-rich ynamides **3k–v** were subjected to the above conditions used for ynamides **3a–j**, a remarkable effect of the electronic properties of the starting alkyne on the product formation was observed. There was no evidence of the presence of type **4** products, with compounds **4k–v** probably undergoing further reaction. To our delight, acetylene derivatives **3k–y** underwent an appealing cyclization/hydroxylation sequence, yielding novel 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5a–j** (Scheme 3). A gram-scale synthesis of **5f** demonstrated the robustness of this methodology. Complete conversion was observed by thin-layer chromatography (TLC) and ^{1}H NMR spectroscopy of the crude reaction mixtures in all cases. However, side reactions were detected on highly activated ynamides **3s** and **3t**, which may be responsible for the



Scheme 3. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 1-aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5**. [a] Major isomer is shown (d.r. = 80:20).

moderate yields of isolated adducts **5i** and **5j**. To test the importance of the steric effects, enantiopure chiral ynamides **3u** and **3v** were prepared and tested. Despite the steric hindrance from the oxazolidinone substituents, aminocyclobutenols **5k** and **5l** were obtained in reasonable yields (Scheme 3). Adduct **5k** was obtained as single enantiomer, whereas adduct **5l** was obtained as an 80:20 diastereomeric mixture. For conclusive assessment of the structure of compounds **5**, an X-ray crystallographic analysis of adduct **5a** was undertaken (Figure 3).[9] On the basis of the structure of aminocyclobutenol **5a**, it must be assumed the participation of adventitious water. The addition of external water was not required, but the inclusion of 1.5 equivalents of H_2O accelerated the process. In view of the fact that all reported methods for accessing cyclobutenols

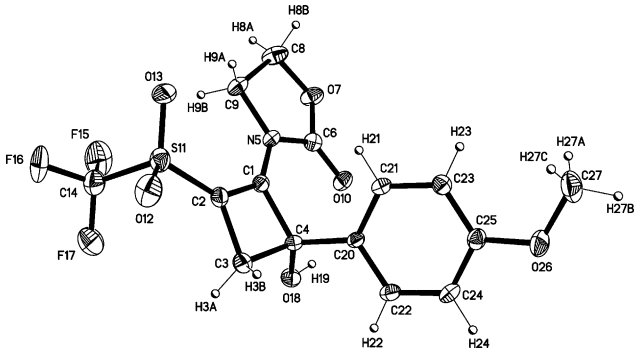
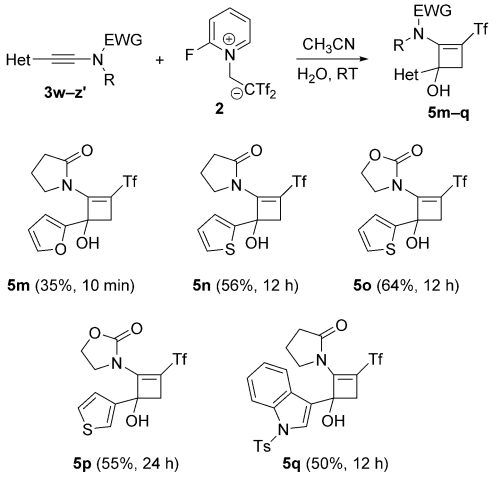


Figure 3. ORTEP representation of 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol (**5a**). Thermal ellipsoids are shown at 50% probability.

should start from cyclobutenones, our protocol could open new horizons for the generation of cyclobutenols in a complementary selective manner by another mechanistically different strategy.

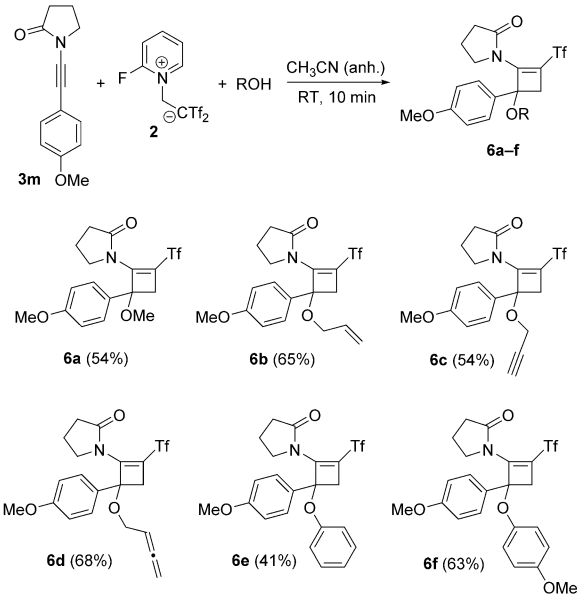
With a number of aromatic-substituted ynamides found to be compatible with the optimized reaction conditions, heteroaromatic rings were investigated to further expand the scope of the reaction (Scheme 4). Ynamides bearing at the C-terminal



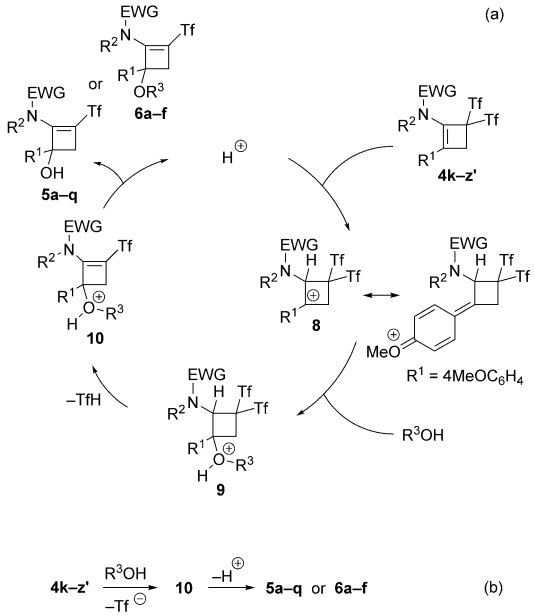
Scheme 4. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 1-hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5**.

several heterocycles including furan, thiophene, and indole did not reduce reactivity of the alkyne. Thus, ynamides **3w–z′** reacted with zwitterion **2** in acetonitrile at room temperature to give aminocyclobutenols **5m–q**. Again, it seems that moderately electron-rich rings have a better performance than highly activated ones (adduct **5m**). Substrate **3z′**, with a large group flanking the ynamide, smoothly underwent the desired transformation. Electronic but not steric variation of the ynamide derivatives played a role in determining the reactivity of alkynes **3**. The absence of hydroxylated products formed from ynamides **3a–j** points to a strong activating effect of electron-donating substituents in ynamides **3k–z′**.

Since the ratio products **4** and **5** may be considered an approximate measure of the relative reactivity of the aminocyclobutene ring towards oxygenated nucleophiles, we decided to perform the reaction of ynamide **3m** with alcohols under otherwise identical conditions. The studies of aminocyclobutene formation with addition of methanol, prop-2-en-1-ol, prop-2-yn-1-ol, and propa-1,2-dien-1-ol demonstrated that the presence of the alcohol moiety exlusively gives aminocyclobutenyl ethers **6a–d**, with the hydroxy group acting as a nucleophile (Scheme 5). Considering the versatility of alkenes, alkynes, and allenes in chemical transformations, cyclobutenes **6b–d** are potentially interesting building blocks for further manipulation. Despite the poor nucleophilicity of phenols, they exhibit ambident reactivity because phenols bear two reaction sites, namely O and C.[10] With regards to selectivity, a major challenge with the use of phenols is to obtain exclusively aryloxyla-



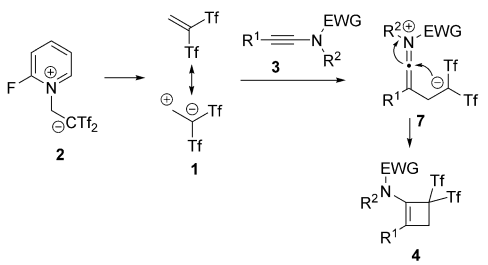
Scheme 5. Uncatalyzed reaction of ynamide **3m** with zwitterion **2** in presence of alcohols. Controlled synthesis of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones **6**.



Scheme 7. Mechanistic explanation for the synthesis of aminocyclobutenes **5** and **6**.

tion or hydroarylation products. Interestingly, the use of phenol and mequinol resulted in the sole formation of the corresponding phenoxy derivatives **6e** and **6f** (Scheme 5). However, the formation in 10% yield of cyclobutenol **5c** together with adduct **6e** revealed that water addition is a competitive reaction in the case of phenol but not for mequinol. It should be noted that aminocyclobutenyl ethers **6a–f** could be isolated and characterized, but they are not as stable as related aminocyclobutenols **5a–l**. The higher stability of cyclobutenols may be ascribed to hydrogen bonding, as indicated by an intramolecular O10···H19 contact in the X-ray diffraction analysis of compound **5a**.

Proposed mechanisms for the formation of aminocyclobutenes **4–6** from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **2** and ynamides **3** are shown in Schemes 6 and 7. It may initially involve the formation of alkene **1**, which may be considered as a resonance hybrid between dipolar and uncharged species, from zwitterion **2**. Next, the stepwise [2+2] cycloaddition reaction between ynamides **3** and the in situ-generated bis(trifluoromethylsulfonyl)ethene



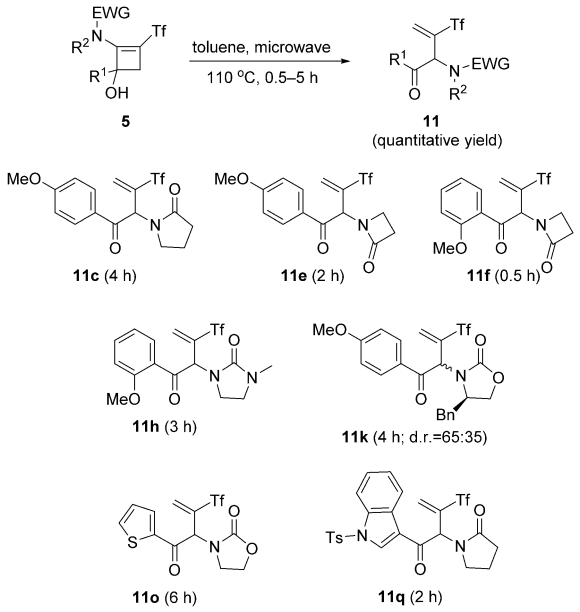
Scheme 6. Mechanistic explanation for the synthesis of aminocyclobutenes **4** from ynamides **3** and zwitterion **2**.

1 should take place, initially leading to the zwitterionic species **7**. The addition product **7** initiates a ring-closing reaction to afford 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **4**. The observed exquisite regiocontrol may arise from the stabilization imparted by the amide group in intermediate **7**, which overrides the effect of the other substituent. For activated ynamides **3k–z′**, the presence of water or alcohols in the reaction media could trigger a rapid nucleophilic attack with concomitant trifluoro(hydrosulfonyl)methane (TfH) elimination, thus leading to the final 1-aryl-2-amino-3-(trifluoromethylsulfonyl)-cyclobut-2-enols **5** or 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones **6**. The conversion of aminocyclobutenes of type **4** into adducts **5** and **6** could be catalyzed by protons (Scheme 7a, top side). A possible pathway for the formation of adducts **5** and **6** may initially involve the formation of carbocations **8** through addition of the proton to the enamine double bond in transient 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamide intermediates **4k–z′**. The driving force of this process may be related to the stabilization of the positive charge in intermediates **8** by electron-rich substituents. Next, intermolecular nucleophilic attack of the oxygen at the benzylic position of cationic species **8** would form an oxonium cation of type **9**. Subsequent loss of TfH-generated species **10** followed by proton release afforded aminocyclobutenol derivatives **5** and **6** with concurrent regeneration of the catalyst.

The treatment of cyclobut-1-enamide **4c** with water under acidic catalysis (HCl, H_2SO_4 or TfOH) did result in complex reaction mixtures. This experimental result, combined with the unusual protonation of enamides at the α-carbon, led us to propose an alternative mechanism for the formation of cyclobutenol derivatives **5** and **6** (Scheme 7b, bottom side). In this way, the direct nucleophilic attack of water or alcohols into the ben-

zylic position should produce intermediate **10** with concomitant Tf^- release.

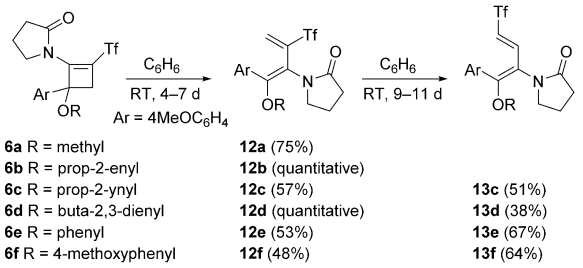
Having developed a direct approach to aminocyclobutenol derivatives **5a–q** and **6a–f** as single isomers from ynamides, we were then interested in using the inherent ring strain[11] of these highly functionalized four-membered carbocycles to perform a selective carbon–carbon bond fragmentation as a new entry to aminoalkenes. Attempts to generate a ring-opened structure from **5c** in refluxing benzene failed. Ring opening of substrate **5c** was successfully accomplished in a microwave reactor by heating a solution of aminocyclobutenol **5c** in toluene at 110 °C (Scheme 8). In this way, α-amino-β,γ-unsaturated



Scheme 8. Ring opening of aminocyclobutenols **5**. Synthesis of 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **11**.

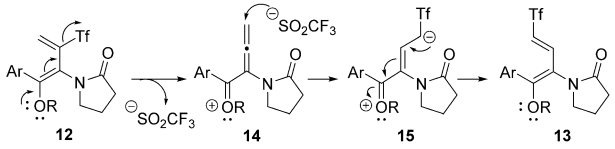
ketone **11c** was cleanly obtained in quantitative yield. Remarkably, this rearrangement was the only operative reaction mode. Accordingly, we carried out the thermally promoted ring opening of several adducts **5** and we smoothly obtained the corresponding 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **11e**, **11f**, **11h**, **11k**, **11o**, and **11q** in quantitative yields. Enantioenriched oxazolidinone **11k** was formed as diasteromeric mixture (d.r. = 65:35) at the newly generated stereogenic center. In all these cases, we once again observed the sole formation of the β,γ-unsaturated ketone (Scheme 8). It should be noted that traditional strategies for the preparation of functionalized β,γ-unsaturated ketones are problematic owing to the possible isomerisation to the α,β-unsaturated ketone.

The utility of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones as precursors for further elaboration is demonstrated in Scheme 9. When adduct **6a** was dissolved in benzene at room temperature, the 4π-electrocyclic ring opening to placeto give the (*Z*)-1-methoxy-1-aryl-3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amine derivative **12a** in



Scheme 9. Ring opening of alkoxycyclobutenamines **6**. Synthesis of functionalized buta-1,3-dien-2-amines **12** and **13**.

good yield. Similarly, the use of compounds **6b–f** as starting materials also efficiently promoted the fragmentation. In each case, (*Z*)-1,3-dienes **12a–f** were formed with total stereoselectivity.[12] The crude reaction mixtures are extremely clean for aminocyclobutenes **6b** and **6d**, giving dienes **12b** and **12d** as the only products detected. Remarkably, the mild conditions of the rearrangement allow the selective formation of diene **12d** without harming the sensitive allene functionality (Scheme 9). Surprisingly, 3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amines **12** can undergo a further reaction in benzene solution through a spontaneous uncatalyzed migration process at room temperature to give (1*Z*,3*E*)-1-alkoxy-1-aryl-4-(trifluoromethylsulfonyl)-buta-1,3-dien-2-amines **13c–f** (Scheme 9). To explain the conversion of **12** into **13**, we must invoke the versatility of sulfone-type groups, which can act as both leaving groups and as nucleophiles.[13] Thus, the critical step in the formal triflyl migration of dienes **12** is the elimination of a trifluoromethanesulfinate anion to afford the allenamide intermediate **14** (Scheme 10). Next, nucleophilic addition of the trifluoromethanesulfinate anion to the terminal allene carbon of **14** generates zwitterionic species **15**, which, after a final rearrangement, produces triflones **13** (Scheme 10).



Scheme 10. Mechanistic explanation for the formal triflyl migration in dienes **12**.

Conclusions

In conclusion, the [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ regioselectively afforded bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with ynamides bearing electron-rich aromatic rings at the C-terminal, an interesting reactivity switch was observed. In such cases, a cyclization/hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. The study of aminocyclobutene formation with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of

functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3-(triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H:, $\delta=0.0$ ppm), or $CDCl_3$ (^{1}H: $\delta=7.27$ ppm; ^{13}C: $\delta=76.9$ ppm), or [D$_6$]acetone (^{1}H: $\delta=2.0$ ppm; ^{13}C: $\delta=206.3$ ppm), or C_6D_6 (^{1}H: $\delta=7.16$ ppm; ^{13}C: $\delta=128.0$ ppm), or CD_3CN (^{1}H: $\delta=2.0$ ppm; ^{13}C: $\delta=118.2$ ppm). Low- and high-resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Synthetic procedures

General procedure for 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides 4a–j: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (1.0 mmol) was added at room temperature to a solution of the appropriate ynamide **3a–j** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until the starting material had disappeared (instantaneous reaction), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenes **4** follow.[14]

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 4a: From ynamide **3a** (30 mg, 0.16 mmol), flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **4a** (72 mg, 94%) as a colorless solid. M.p. 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.45$ (m, 5H, CH^{Ar}), 4.52 (dd, 2H, $J=8.7$, 7.1 Hz, CH_2), 4.07 (dd, 2H, $J=8.9$, 6.9 Hz, CH_2), 3.53 ppm (s, 2H, CH_2-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=154.0$ (C=O), 147.8 (C=*C*-N), 131.9 (CH^{Ar}), 129.1 (*C*=C-N), 128.9 (2CH^{Ar}), 128.4 (2CH^{Ar}), 119.8 (q, *J*(C,F) = 331.3 Hz, $2CF_3$), 117.9 (C^{Ar-q}), 88.4 (CTf_2), 63.1 (CH_2), 44.8 (CH_2), 31.8 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-69.87$ ppm (s, 6F, $2CF_3$); IR ($CHCl_3$): $\tilde{\nu}=1771$ (C=O), 1669 (C=C), 1380, 1104 (O=S=O), 1201 cm^{-1} (C–F); HRMS (ES): calcd for $C_{15}H_{11}NO_6S_2F_6$ $[M]^+$: 478.9932; found: 478.9928.

General procedure for 1-substituted-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols 5a–q: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (1.0 mmol) and water (1.5 mmol) were sequentially added at room temperature to a solution of the appropriate ynamide **3k–z′** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until the starting material had disappeared (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenols **5** follow.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 5a: From ynamide **3k** (50 mg, 0.23 mmol), flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **5a** (60 mg, 64%) as a colorless solid. M.p. 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.32$ (m, 2H, 2CH^{Ar}), 6.91 (m, 2H, 2CH^{Ar}), 4.58 (m, 3H, CH_2, OH), 4.36 (m, 1H, CH*H*), 4.22 (m, 1H, C*H*H), 3.82 (s, 3H, OCH_3), 3.19 (d, 1H, $J=10.4$ Hz, CH*H*-*cyclobutene*), 2.88 ppm (d, 1H, $J=10.4$ Hz, C*H*H-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=159.4$ (C^{Ar-q}–OCH_3), 155.3 (C=O), 154.2 (C=*C*-N), 132.1 (C^{Ar-q}), 125.0 (2CH^{Ar}), 119.9 (q, *J*(C,F) = 325.6 Hz, CF_3), 114.2 (2CH^{Ar}), 101.1 (*C*=C-N), 77.8 (C^q-OH), 64.4 (CH_2), 55.2 (OCH_3), 45.4 (CH_2), 44.8 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-78.34$ ppm (s, 3F, CF_3); IR ($CHCl_3$): $\tilde{\nu}=3483$ (OH), 1770 (C=O), 1620 (C=C), 1398, 1127 (O=S=O), 1198 cm^{-1} (C–F); HRMS (ES): calcd for $C_{15}H_{14}NO_6SF_3$ $[M]^+$: 393.0494; found: 393.0478. X-ray data of **5a**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{15}H_{14}F_3NO_6S$ ($M_r=393.33$); orthorhombic; space group = *Pbca*; $a=8.8736(6)$, $b=19.2477(14)$, $c=39.638(3)$ Å; $\alpha=90$, $\beta=90$, $\gamma=90°$; $V=6770.1(8)$ Å^3; $Z=16$; cd = 1.544 mg m^{-3}; $\mu=0.256$ mm^{-1}; F(000) = 3232. 5974 ($R_{int}=0.0939$) independent reflections were collected on a Bruker Smart CCD difractomer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) operating at 50 kV and 35 mA. The structure was solved by direct methods and was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final *R* indices [$I>2\sigma(I)$] values were *R*1 (reflns obsd) = 0.0513 (2529), *wR*2 (all data) = 0.1533.[9]

General procedure for 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones 6a–f: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (0.1 mmol) and the corresponding alcohol or phenol (0.15 mmol) were sequentially added at room temperature to a solution of ynamide **3m** (0.1 mmol) in acetonitrile (1 mL). The reaction was stirred at room temperature until the starting material had disappeared (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenyl ethers **6** follow.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 6d: From ynamide **3m** (30 mg, 0.139 mmol), flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **6d** (42 mg, 68%) as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): $\delta=7.61$ (m, 2H, 2CH^{Ar}), 6.79 (m, 2H, 2CH^{Ar}), 5.34 (m, 1H, *CH*=·=CH_2), 4.65 (m, 2H, CH=·=*C*H_2), 4.11 (m, 1H, OCH*H*), 3.97 (m, 1H, OC*H*H), 3.38 (m, 2H, CH_2), 3.28 (m, 4H, OCH_3, CH*H*-*cyclobutene*), 2.95 (d, 1H, $J=11.2$ Hz, C*H*H-*cyclobutene*), 1.38 (m, 2H, CH_2), 0.87 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): $\delta=209.2$ (C=*C*=C), 172.3 (C=O), 159.8 (C^{Ar-q}–OCH_3), 156.1 (C=*C*-N), 130.6 (C^{Ar-q}), 126.8 (2CH^{Ar}), 120.9 (q, *J*(C,F) = 326.9 Hz, CF_3), 114.1 (2CH^{Ar}), 100.5 (*C*=C-N), 88.6 (*CH*=C=CH_2), 83.4 (C^{Cq}-OCH_2CH=C=CH_2), 76.3 (CH=C=*C*H_2), 63.5 (OCH_2), 54.8 (OCH_3), 48.0 (CH_2), 42.2 (CH_2), 29.6 (CH_2), 18.0 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): $\delta=-77.64$ ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}=1958$ (C=C=C), 1761 (C=O), 1596 (C=C), 1365, 1112 (O=S=O), 1208 (C–O), 1185 cm^{-1} (C–F); HRMS (ES): calcd for $C_{20}H_{20}NO_5SF_3$ $[M]^+$: 443.1014; found: 443.1016.

General procedure for 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones 11: A stirred solution of the appropriate aminocyclobutenol **5** (0.1 mmol) in toluene (2.0 mL) was heated at 110 °C under

microwave irradiation until the starting material had disappeared (TLC). The reaction was allowed to cool to room temperature and concentrated under vacuum. Further purification was not necessary. Spectroscopic and analytical data for pure forms of compound **11 c** follow.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 11 c: From aminocyclobutenol **5 c** (36 mg, 0.09 mmol), compound **11 c** (36 mg, quantitative yield) was obtained as a green pale oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.99 (m, 2H, 2CH^{Ar}), 6.97 (m, 2H, 2CH^{Ar}), 6.95 (d, 1H, J = 1.9 Hz = CH*H*), 6.75 (s, 1H, CH-N), 6.55 (s, 1H, =C*H*H), 3.89 (s, 3H, OCH_3), 3.60 (m, 1H, CH*H*), 3.35 (m, 1H, C*H*H), 2.45 (m, 2H, CH_2), 2.07 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 191.1 (C=O), 175.9 (NC=O), 164.7 (C^{Ar-q}–OCH_3), 140.1 (=CH_2), 139.2 (=*C*-Tf), 131.3 (2CH^{Ar}), 126.5 (C^{Ar-q}), 119.6 (q, J(C,F) = 327.1 Hz, CF_3), 114.4 (2CH^{Ar}), 55.6 (OCH_3), 53.7 (CH-N), 44.8 (CH_2), 30.5 (CH_2), 18.4 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −77.41 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1690 (NC=O, C=O), 1601 (C=C), 1366, 1104 (O=S=O), 1213 cm^{-1} (C–F); HRMS (ES): calcd for $C_{16}H_{16}NO_5SF_3$ $[M]^+$: 391.0701; found: 391.0698.

General procedure for the synthesis of buta-1,3-dien-2-amines 12: A solution of the appropriate alkoxycyclobutenamine **6** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until the starting material had disappeared (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **12** follow.

Buta-1,3-dien-2-amine 12 a: From aminocyclobutenyl ether **6 a** (20 mg, 0.049 mmol), flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **12 a** (15 mg, 75%) as a bright yellow oil. ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.08 (m, 2H, 2CH^{Ar}), 6.56 (m, 2H, 2CH^{Ar}), 6.27 (s, 1H, =CH*H*), 6.08 (s, 1H, =C*H*H), 3.59 (t, 2H, J = 7.1 Hz, CH_2), 3.14 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 2.08 (t, 2H, J = 8.1 Hz, CH_2), 1.56 ppm (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 175.0 (C=O), 161.0 (C^{Ar-q}–OCH_3), 159.1 (C=*C*-N), 142.0 (=CH_2), 140.7 (*C*=C-N), 131.5 (2CH^{Ar}), 123.3 (C^{Ar-q}), 120.5 (q, J(C,F) = 327.8 Hz, CF_3), 114.3 (2CH^{Ar}), 112.0 (=*C*-Tf), 56.8 (OCH_3), 54.7 (OCH_3), 48.0 (CH_2), 30.6 (CH_2), 19.0 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −78.15 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1698 (C=O), 1606 (C=C), 1360, 1115 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): calcd for $C_{17}H_{18}NO_5SF_3$ $[M]^+$: 405.0858; found: 405.0868.

General procedure for the synthesis of buta-1,3-dien-2-amines 13: A solution of the appropriate buta-1,3-dien-2-amine **12** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until the starting material had disappeared (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **13** follow.

Buta-1,3-dien-2-amine 13 e: From buta-1,3-dien-2-amine **12 e** (14 mg, 0.029 mmol), flash chromatography of the residue using hexanes/ethyl acetate (8:2→7:3) as eluent gave compound **13 e** (9.4 mg, 67%) as a bright yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.91 (d, 1H, J = 14.7 Hz, Tf–CH=C*H*), 7.13 (m, 2H, 2CH^{Ar}), 6.96 (m, 2H, 2CH^{Ar}), 6.87 (m, 2H, 2CH^{Ar}), 6.65 (m, 1H, CH^{Ar}), 6.42 (m, 2H, 2CH^{Ar}), 6.32 (d, 1H, J = 14.7 Hz, Tf–*CH*=CH), 2.95 (s, 5H, OCH_3, CH_2), 1.85 (t, 2H, J = 8.0 Hz, CH_2), 1.20 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 174.0 (C=O), 165.0 (C=*C*-N) 162.4 (C^{Ar-q}–OCH_3), 156.3 (C^{Ar-q}–O-C=), 150.0 (Tf–CH=CH), 132.9 (2CH^{Ar}), 129.7 (2CH^{Ar}), 124.3 (CH^{Ar}), 123.2 (C^{Ar-q}), 120.8 (q, J(C,F) = 324.7 Hz, CF_3), 119.6 (2CH^{Ar}), 119.2 (C=C-N), 114.4 (2CH^{Ar}), 113.5 (Tf–CH=CH), 54.7 (OCH_3), 46.8 (CH_2), 30.1 (CH_2), 18.9 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −78.12 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1705 (C=O), 1580 (C=C), 1358, 1117 (O=S=O), 1205 cm^{-1} (C–F); HRMS (ES): calcd for $C_{22}H_{20}NO_5SF_3$ $[M]^+$: 467.1014; found: 467.1019.

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Keywords: alkynes · amides · cyclization · fluorine · small ring systems

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Disubstituted Cyclobut-2-en-1-ones |*Hot Paper*|

Convenient Access to 2,3-Disubstituted-cyclobut-2-en-1-ones under Suzuki Conditions and Their Synthetic Utility

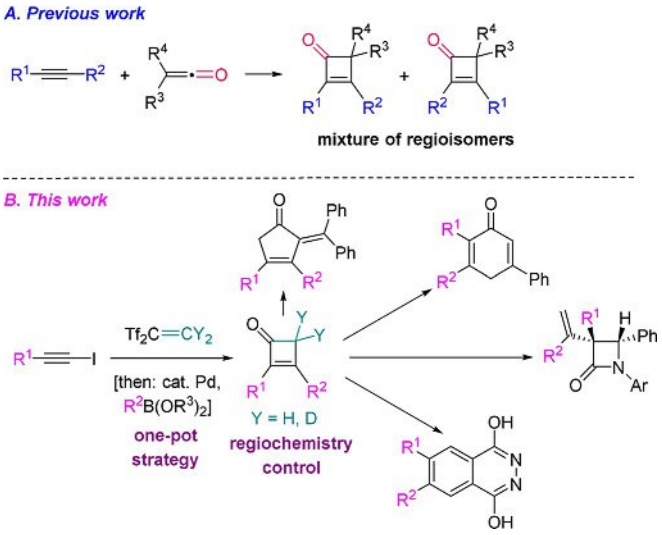
Benito Alcaide,*[a] Pedro Almendros,*[b] and Carlos Lázaro-Milla[a]

In memory of Professor Pedro Molina

Abstract: A regioselective synthesis of general applicability has been designed for the one-pot preparation of 2,3-disubstituted-cyclobutenones from iodoalkynes through cyclobutenylation, Suzuki CC coupling, and ketone formation. This one-pot methodology has been applied to the selective synthesis of an orally active cyclooxygenase II inhibitor. Furthermore, the obtained cyclobut-2-en-1-ones were used as synthons in several transformations, such as, the preparation of β-lactams, phthalazines, cyclohexa-2,5-dien-1-ones, and cyclopent-3-en-1-ones.

Introduction

The cyclobut-2-en-1-one motif is present in several natural products such as in alterbrassicene A, which displays enzymatic inhibitor activity.[1] In addition, the relevance of cyclobutenones as synthetic intermediates has been broadly identified in organic synthesis because ring cleavage of the four-membered carbocycle is enhanced by ring strain.[2] The classical method for the synthesis of the cyclobutenone skeleton takes advantage of the [2+2] cycloaddition reaction between alkynes and in situ-generated ketenes (Scheme 1 A).[3] However, regioselectivity challenges occur and isomers may be generated during the ring formation reaction. Consequently, novel methods for the controlled synthesis of cyclobutenones are highly desirable. Herein, we present a one-pot synthesis of cyclobutenones from iodoalkynes through sequential bis(triflyl)cyclobutenylation and Suzuki reaction with concomitant ketone formation (Scheme 1 B). This procedure revealed exquisite regioselectivity, offering a complement to the state-of-the-art available methodology. In addition, the obtained 2,3-disubstituted-cyclobut-2-en-1-ones were used as useful synthons in several transformations (Scheme 1 B), such as the preparation of a selective and orally active cyclooxygenase II inhibitor.



Scheme 1. Known methodology and current synthetic route towards the cyclobutenone motif, and associated synthetic utility.

Results and Discussion

We have recently described the facile synthesis of bis(triflyl)iodocyclobutenes **3** through the reaction of iodoalkynes **1** and Yanai's reagent **2**.[4,5] We decided to set up conditions for the cross-coupling reactions of readily available adducts **3**, which should functionalize the cyclobutene core[6] and may allow further ketone formation. This protocol should provide a regiocontrolled access to the 2,3-disubstituted-cyclobut-2-en-1-one scaffold through the use of the bis(triflyl)methane moiety as a masked ketone. With the aim of validating our strategy, Pd-catalyzed conditions were applied for the C–C coupling of bis(triflyl)iodocyclobutenes **3**. Unfortunately, iodocyclobutenes **3** remained unreactive under Negishi conditions. Interestingly, Heck and Stille reactions proceeded well (Scheme 2 and Scheme 3). Noteworthy, concurrent ketone formation was ob-

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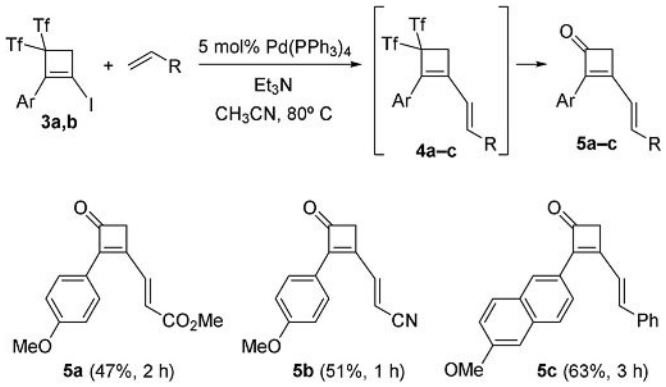
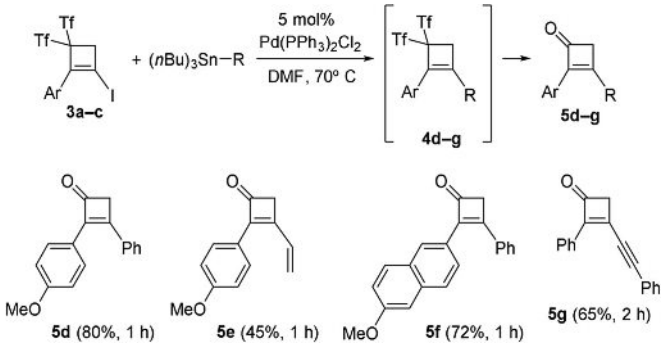
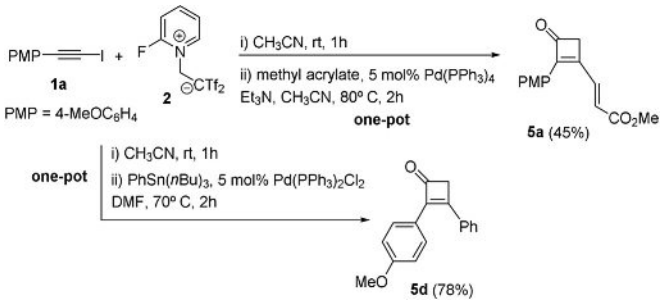


Scheme 2. Palladium-catalyzed reaction of bis(triflyl)iodocyclobutenes **3a**,**b** with alkenes. Regiocontrolled synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones **5a**–**c**.



Scheme 3. Palladium-catalyzed reaction of bis(triflyl)iodocyclobutenes **3a**–**c** with stannanes. Regiocontrolled synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones **5d**–**g**.

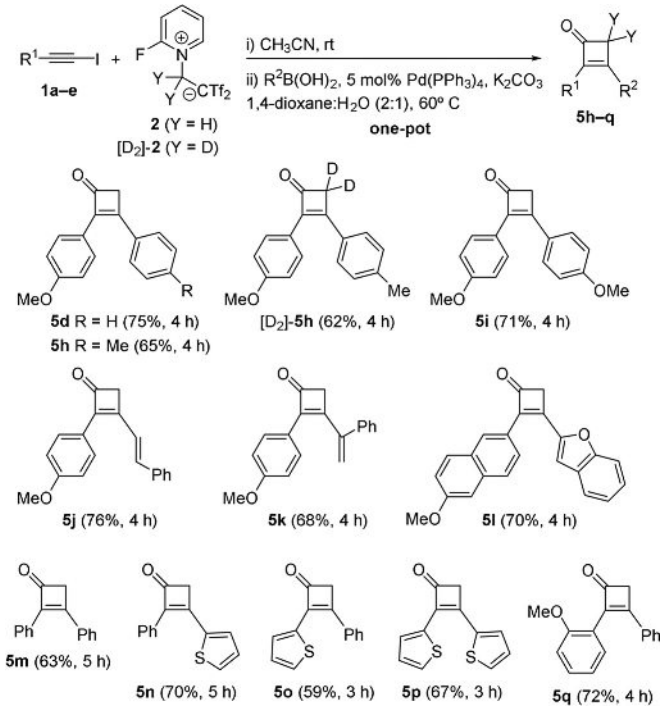


Scheme 4. One-pot preparation of 2,3-disubstituted-cyclobut-2-en-1-ones **5a**,**d**.

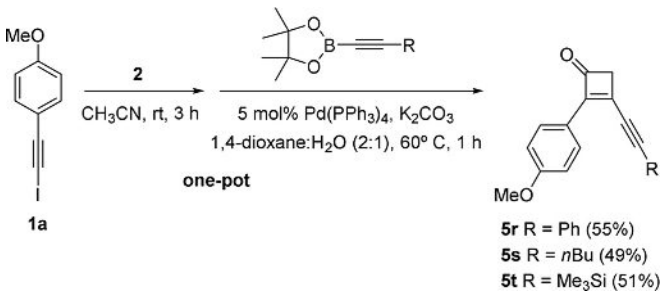
served to deliver 2,3-disubstituted-cyclobut-2-en-1-ones **5**, which should imply the participation of adventitious water in the hydrolysis step of the non-isolable bis(triflyl)cyclobutenes **4**.

A one-pot iodocyclobutene formation and C–C coupling process would be more convenient, but the one-pot alkyne activation/cross-coupling/ketone formation reactions present several reactivity challenges. Thus, treatment of iodoalkynes **1** with Yanai's reagent **2** in acetonitrile at room temperature was followed by solvent removal. The unpurified bis(triflyl)iodocyclobutenes **3** were combined with the appropriate cross-coupling reagent by following the standard procedures. Interestingly, Heck and Stille conditions were amenable for the one-pot protocol starting from iodoalkyne **1a** (Scheme 4). Taking into account the high purity of crude bis(triflyl)iodocyclobutenes **3**, we believe that Suzuki conditions would be even more satisfactory for operating a one-pot procedure.[7] Consequently, we used Suzuki conditions in the cross-coupling of in situ-generated bis(triflyl)iodocyclobutenes **3** through the utilization of a one-pot procedure. Delightfully, starting from the appropriate iodoalkyne **1** and Yanai's reagent **2**, followed by the addition of the corresponding boronic acid and the palladium catalyst, the one-pot protocol can be efficiently accomplished. In this way, different functionalized 2,3-disubstituted-cyclobut-2-en-1-ones **5** were directly obtained in good yields from iodoalkynes **1** without laborious isolation of any intermediates (Scheme 5 and Scheme 6), which in terms of simplicity and effectiveness is more appealing. This simple and versatile one-pot procedure is successfully applied to the convenient preparation of 2,3-diaryl-cyclobut-2-en-1-ones, 2-aryl-3-alkenyl-cyclobut-2-en-1-ones, and 2-aryl-3-alkynyl-cyclobut-2-en-1-ones. In the last case, alkynylboronic acid pinacol esters were used as the cross-coupling partners (Scheme 6). Gratifyingly, a salient feature of the present method is the facile access to deuterated compounds such as 2-(4-methoxyphenyl)-3-(4-tolyl)cyclobut-2-en-1-one-4,4-d_2 [D_2]-**5h** (Scheme 5).[8]

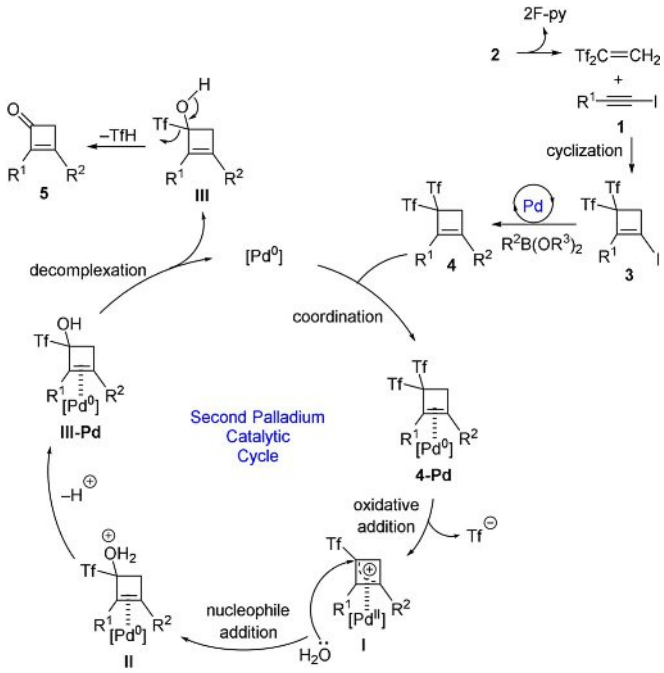
In Scheme 7, we propose a reaction mechanism for our one-pot sequence. Initially, iodoalkynes **1** are converted into bis(triflyl)iodocyclobutenes **3** by cyclization reaction with the in situ-generated 1,1-bis[(trifluoromethyl)sulfonyl]ethene. Adducts **3** further react with boronic acids or boronic acid pinacol esters



Scheme 5. One-pot controlled preparation of 2,3-diaryl-cyclobut-2-en-1-ones **5h**,**i**, [D_2]-**5h**, **5l**–**q**, and 2-aryl-3-alkenyl-cyclobut-2-en-1-ones **5j**,**k**.



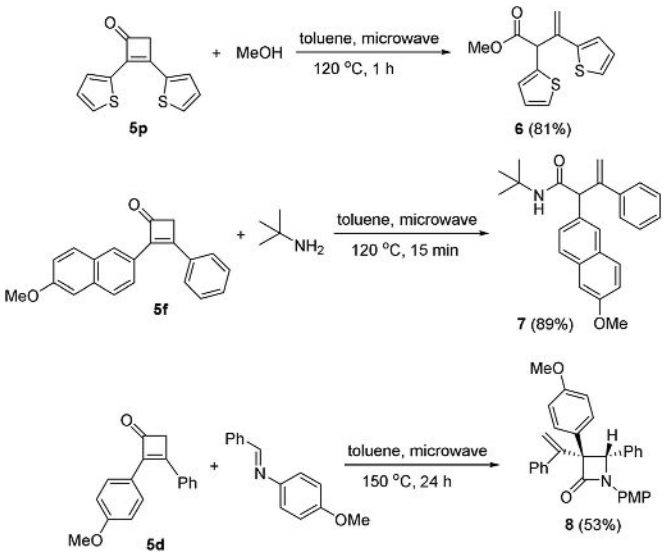
Scheme 6. One-pot controlled preparation of 2-aryl-3-alkynyl-cyclobut-2-en-1-ones **5r–t**.



Scheme 7. Proposed reaction pathway for the one-pot preparation of 2,3-disubstituted-cyclobut-2-en-1-ones **5** from iodoalkynes **1** under Suzuki conditions.

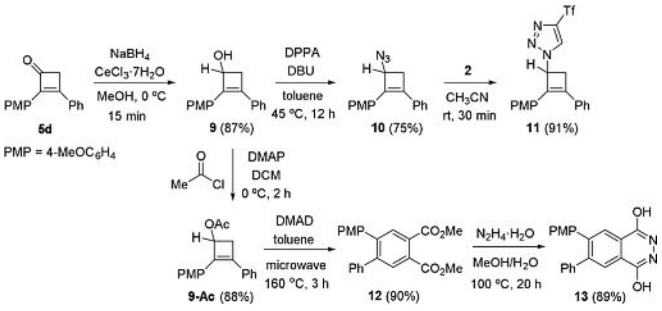
under Pd-catalyzed conditions to complete the first palladium catalytic cycle with concurrent formation of intermediate bis-(triflyl)cyclobutenes **4**. The $Pd(PPh_3)_4$ also facilitates the formation of Tf-cyclobutenol intermediates **III** through an allylic substitution reaction (second catalytic cycle). After coordination, the Pd^0 species should promote oxidative addition with the allyl substrates **4**, which bear a leaving group (Tf) by generation of π-allyl palladium species **I**. These formed Pd^{II} species are very reactive and undergo a selective nucleophilic attack by water at the 1-position to form intermediates **II**, which after proton release and decomplexation should liberate Tf-cyclobutenols **III** with concomitant regeneration of the palladium catalytic species. Finally, TfH loss gives rise to the observed 2,3-disubstituted-cyclobut-2-en-1-ones **5**.

Taking into account the inherent ring strain associated with the cyclobutenone ring, we next focused on the transformation of the above-prepared 2,3-disubstituted-cyclobut-2-en-1-ones **5**. In the event, thermal ring opening and subsequent trapping of the resulting ketene was attained in the presence of several reagents such as methanol, *tert*-butylamine, and *N*-(4-methoxyphenyl)-1-phenylmethanimine (Scheme 8). Worthy of note, the β-lactam **8**[9] was obtained in a totally stereoselective fashion through transannulation of cyclobutenone **5d** (Scheme 8).



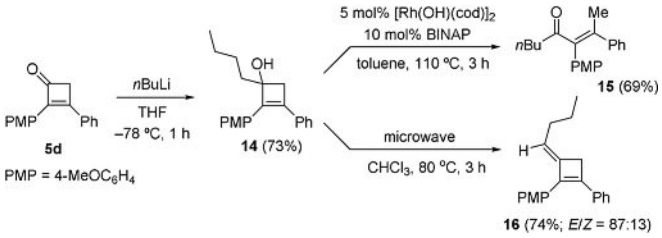
Scheme 8. Ring-opening or transannulation reactions of cyclobutenones **5**. Controlled preparation of 2,3-disubstituted-but-3-enoate **6**, 2,3-disubstituted-but-3-enamide **7**, and β-lactam **8**.

As an additional application of the prepared carbocycles **5**, the reduction of cyclobut-2-en-1-one **5d** to cyclobutenol **9** and its further synthetic utility were attempted (Scheme 9). Cyclobutenyl-triazole **11** and the tetrasubstituted benzene **12** were obtained in good overall yields. The convenient preparation of cyclobutenyl-triazole **11** was accomplished from cyclobutenol **9** through sequential treatment with diphenyl phosphoryl azide (DPPA) and Yanai's reagent **2**.[10] The ring-expanded product **12** was formed very well from acetate **9-Ac** by thermal cascade reaction between an in situ formed diene and dimethylacetylene dicarboxylate (DMAD). The dimethyl phthalate derivative **12** was treated with hydrazine hydrate and converted into the 6,7-disubstituted-phthalazine-1,4-diol **13**.[11] We



Scheme 9. Reduction and ring expansion reactions of cyclobutenone **5d**. Controlled preparation of cyclobutenyl-triazole **11** and phthalazine derivative **13**.

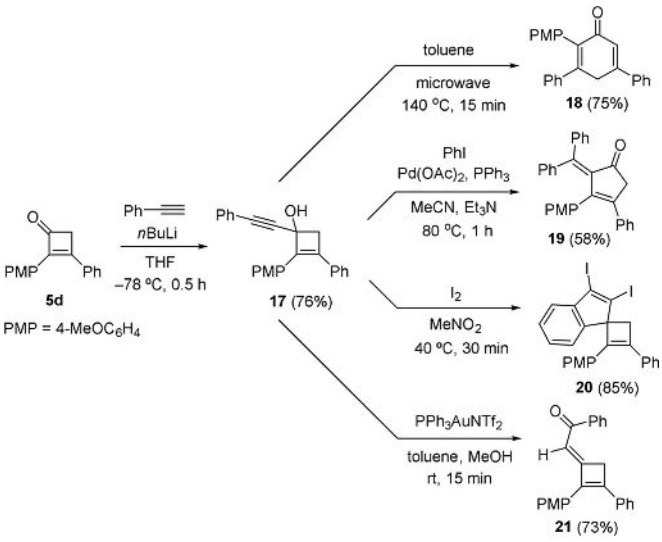
also explored the addition of organometallic reagents to the cyclobutenone core and associated ring transformations. A 73% yield of quaternary cyclobutenol **14** was obtained after the reaction of cyclobutenone **5d** with BuLi (Scheme 10). The α,β-unsaturated ketone **15**, arising from a rhodium-catalyzed ring-opening reaction of **14**, was achieved as a single *Z*-isomer. A dehydration occurred by heating **14** at reflux in chloroform to afford the cyclobutadiene **16** (Scheme 10).



Scheme 10. Alkenylation and ring-opening reactions of cyclobutenone **5d**. Controlled preparation of α,β-unsaturated ketone **15** and cyclobutadiene **16**.

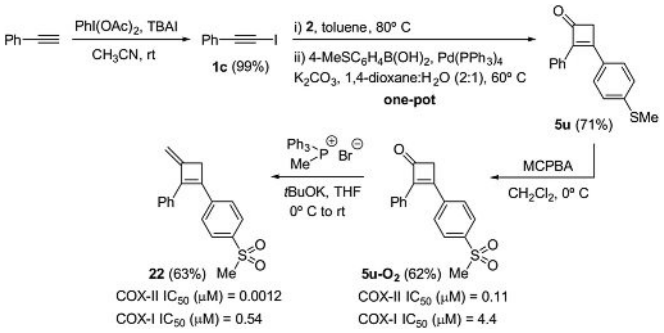
Next, we proposed cyclobutene-tethered alkynol **17**, which was readily prepared from cyclobut-2-en-1-one **5d** through the reaction with lithium phenylacetylide, as a platform for the achievement of different structural motifs (Scheme 11). Interestingly, the thermal two-carbon ring enlargement was easily accomplished to form trisubstituted cyclohexa-2,5-dien-1-one **18**. Also, the synthesis of trisubstituted cyclopent-3-en-1-one **19** based on a Pd-catalyzed C–C coupling one-atom ring expansion cascade was achieved. In addition, spirocyclic cyclobutene **20** and the Meyer–Schuster rearranged adduct **21** were smoothly synthesized.

The efficiency of this novel cyclobutenone construction method paved the way for the preparation of bioactive products bearing related structural motifs. As a proof of concept,



Scheme 11. Alkenylation, spirocyclization, and ring-expansion reactions of cyclobutenone **5d**. Controlled preparation of cyclohexa-2,5-dien-1-one **18**, cyclopent-3-en-1-one **19**, spirocyclic cyclobutene **20**, and cyclobutadienone **21**.

we directed our efforts towards the synthesis of cyclobutadiene **22**, an orally active cyclooxygenase (COX) II inhibitor [COX-II $IC_{50} = 0.0012$ μM; COX-I $IC_{50} = 0.54$ μM], which has been previously prepared from phenylacetylene in an overall 1.7% yield.[12] Our proposal was based on the straightforward synthesis of 2,3-disubstituted-cyclobut-2-en-1-one **5u** followed by selective *S*-oxidation and alkenylation reactions. In this way, the synthesis of compound **22** was reached from phenylacetylene in an overall 27% yield (Scheme 12).



Scheme 12. Efficient preparation of the selective cyclooxygenase (COX) inhibitor **22**.

Conclusion

We have developed a regioselective one-pot synthesis of cyclobutenones from iodoalkynes through sequential bis(triflyl)cyclobutenylation and Suzuki reaction with concomitant ketone formation. This one-pot methodology has been used for the efficient synthesis of a selective and orally active cyclooxygenase II inhibitor. In addition, the obtained 2,3-disubstituted-cyclobut-2-en-1-ones were used as useful synthons in several transformations such as for the preparation of 2,3-disubstituted-but-3-enoates, β-lactams, phthalazines, α,β-unsaturated ketones, cyclobutadienes, cyclohexa-2,5-dien-1-ones, and cyclopent-3-en-1-ones.

Experimental Section

General methods

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded with a Bruker Avance AMX-700, Bruker AMX-500, or Bruker Avance-DPX 300 spectrometer. NMR spectra were recorded in $CDCl_3$, C_6D_6, CD_3CN, or [D_6]DMSO solutions, or as otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm), or [D_6]DMSO (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Chemical shifts in ^{19}F are given in ppm relative to (trifluoromethyl)benzene ($C_6H_5CF_3$) in $CDCl_3$ (^{19}F, −63.7 ppm). Low- and high-resolution mass spectra were taken with an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer by using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded with a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General procedure for the palladium-catalyzed Heck reaction/ketone formation of bis(triflyl)iodocyclobutenes 3: Synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones 5a–c

A solution of the appropriate bis(triflyl)iodocyclobutene **3** (1.0 mmol), the corresponding alkene (3.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol, 5.0 mol%), and triethylamine (3.0 mmol) in acetonitrile (10 mL) was heated in a sealed tube at 80 °C until the disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3×15 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **5a–c** are given below and in the Supporting Information.[13]

Methyl (*E*)-3-(2-(4-methoxyphenyl)-3-oxocyclobut-1-en-1-yl)acrylate 5a: From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **3a**, and after flash chromatography of the residue by using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **5a** (11 mg, 47%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 8.00 (d, 1H, J = 15.3 Hz, CH=CH), 7.72 (m, 2H, $2CH^{Ar}$), 6.61 (m, 2H, $2CH^{Ar}$), 5.80 (d, 1H, J = 15.3 Hz, CH=*CH*), 3.43 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 2.86 ppm (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 188.0 (C=O), 166.0 (C=OO), 161.1 (C^{Ar-q}–OCH_3), 151.9 (C=C), 147.5 (C=C), 134.1 (HC=CH), 129.9 ($2CH^{Ar}$), 128.0 (HC=CH), 122.9 (C^{Ar-q}), 114.7 ($2CH^{Ar}$), 54.7 (OCH_3), 51.5 (OCH_3), 48.9 ppm (CH_2); IR (CH_2Cl_2): ν = 1744 (C=O), 1726 (C=OO) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.09649; found: 259.09772.

General procedure for the palladium-catalyzed Stille reaction/ketone formation of bis(triflyl)iodocyclobutenes 3: Synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 5d–g

A solution of the appropriate bis(triflyl)iodocyclobutene **3** (1.0 mmol), the corresponding stannane (5.0 mmol), and $Pd(PPh_3)_2Cl_2$ (0.05 mmol, 5.0 mol%) in *N*,*N*-dimethylformamide (10 mL) was heated in a sealed tube at 70 °C until the disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3×15 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **5d–g** are given below and in the Supporting Information.

2-(4-Methoxyphenyl)-3-phenylcyclobut-2-en-1-one 5d: From 50 mg (0.09 mmol) of bis(triflyl)iodocyclobutene **3a**, and after flash chromatography of the residue by using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **5d** (18 mg, 80%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.77 (m, 2H, $2CH^{Ar}$), 7.68 (m, 2H, $2CH^{Ar}$), 7.48 (m, 3H, $3CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 3.85 (s, 3H, OCH_3), 3.62 ppm (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 188.4 (C=O), 159.9 (C=C), 159.8 (C^{Ar-q}–OCH_3), 141.3 (C^{Ar-q}), 132.7 (C=C), 131.2 (CH^{Ar}), 129.1 ($2CH^{Ar}$), 128.8 ($2CH^{Ar}$), 128.7 ($2CH^{Ar}$), 122.3 (C^{Ar-q}), 114.1 ($2CH^{Ar}$), 55.3 (OCH_3), 49.5 ppm (CH_2); IR ($CHCl_3$): ν = 1739 (C=O), 1607 (C=C) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{15}O_2$ $[M+H]^+$: 251.10666; found: 251.10776.

General procedure for the one-pot synthesis of 2-aryl-3-alkenyl-cyclobut-2-en-1-ones 5 by using Heck reaction conditions

Yanais' reagent **2** (0.1 mmol) was added at 20 °C to a solution of the appropriate alkyne **1** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until the disappearance of the starting material (TLC). The corresponding alkene (0.3 mmol), $Pd(PPh_3)_4$ (0.005 mmol, 5.0 mol%), and triethylamine (0.3 mmol) in acetonitrile (0.5 mL) were added to the above crude bis(triflyl)cyclobutene **3**. The resulting solution was heated in a sealed tube at 80 °C until the disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3×5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds.

General procedure for the one-pot synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 5 by using Stille reaction conditions

Yanais' reagent **2** (0.1 mmol) was added at room temperature to a solution of the appropriate alkyne **1** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until the disappearance of the starting material (TLC). After removal of the acetonitrile, the corresponding stannane (0.5 mmol), and $Pd(PPh_3)_2Cl_2$ (0.005 mmol, 5.0 mol%) in *N*,*N*-dimethylformamide (2 mL) were added to the above crude bis(triflyl)cyclobutene **3**. The resulting solution was heated in a sealed tube at 70 °C until the disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3×5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds.

General procedure for the one-pot synthesis of 2,3-disubstituted-cyclobut-2-en-1-ones 5h–u and [D$_2$]-5h by using Suzuki reaction conditions

Yanais' reagent **2** or deuterated Yanais' reagent [D_2]-**2** (0.1 mmol) was added at room temperature to a solution of the appropriate alkyne **1** (0.1 mmol) in acetonitrile (2 mL). The reaction was stirred at room temperature until the disappearance of the starting material (TLC). After removal of the acetonitrile, the corresponding boronic acid or boronic ester (0.15 mmol), K_2CO_3 (0.3 mmol), and 1,4-dioxane/water (2:1, 1.5 mL) were added to the above crude bis(triflyl)cyclobutene **3**. The reaction was stirred at room temperature for 10 min. Then, $Pd(PPh_3)_4$ (0.005 mmol, 5.0 mol%) was added and the resulting mixture was heated in a sealed tube at 60 °C until the disappearance of the starting material (TLC). The reaction mixture was allowed to cool to room temperature and was extracted with ethyl acetate (3×5 mL). The combined organic extract was dried over $MgSO_4$, and the desiccant was removed by filtration. After removal of the solvent under vacuum, the residue was purified by column chromatography on silica gel to give analytically pure compounds. Spectroscopic and analytical data for products **5h–u** and [D_2]-**5h** follow.

2-(4-Methoxyphenyl)-3-(*p*-tolyl)cyclobut-2-en-1-one 5h: From 80 mg (0.14 mmol) of iodoalkyne **1a**, and after flash chromatography of the residue by using hexanes/ethyl acetate (97:3→9:1) as

eluent gave compound **5h** (24 mg, 65%) as a colorless solid; m.p.: 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.67$ (m, 4H, 4 CH^{Ar}), 7.27 (m, 2H, 2 CH^{Ar}), 6.94 (m, 2H, 2 CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 2.43 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 188.5$ (C=O), 160.0 (C=C), 159.8 (C^{Ar-q}–OCH_3), 142.1 (C^{Ar-q}), 140.4 (C=C), 130.0 (C^{Ar-q}), 129.5 (2 CH^{Ar}), 129.0 (2 CH^{Ar}), 128.8 (2 CH^{Ar}), 122.5 (C^{Ar-q}), 114.0 (2 CH^{Ar}), 55.3 (OCH_3), 49.4 (CH_2), 21.7 ppm (CH_3); IR ($CHCl_3$): $\nu = 1741$ (C=O), 1607 (C=C), 1249 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{17}O_2$ $[M+H]^+$: 265.12231; found: 265.12146.

2-(4-Methoxyphenyl)-3-(*p*-tolyl)cyclobut-2-en-1-one-4,4-d$_2$ [D$_2$]-5h: From 50 mg (0.09 mmol) of iodoalkyne **1a**, and after flash chromatography of the residue by using hexanes/ethyl acetate (95:5) as eluent gave compound [D$_2$]-**5h** (15 mg, 62%) as a colorless solid; m.p.: 103–105 °C; ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C): $\delta = 7.67$ (m, 4H, 4 CH^{Ar}), 7.27 (m, 2H, 2 CH^{Ar}), 6.94 (m, 2H, 2 CH^{Ar}), 3.85 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 2.43 ppm (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C): $\delta = 188.5$ (C=O), 159.9 (C=C), 159.8 (C^{Ar-q}–OCH_3), 142.1 (C^{Ar-q}), 140.6 (C=C), 130.0 (C^{Ar-q}), 129.5 (2 CH^{Ar}), 129.0 (2 CH^{Ar}), 128.9 (2 CH^{Ar}), 122.5 (C^{Ar-q}), 114.0 (2 CH^{Ar}), 55.3 (OCH_3), 48.8 (m, CD_2), 21.7 ppm (CH_3); D(^{2}H) NMR (107 MHz, $CDCl_3$, 25 °C): $\delta = 3.56$ ppm (s, 2D, CD_2); IR ($CHCl_3$): $\nu = 1740$ (C=O), 1608 (C=C), 1247 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{14}D_2NaO_2$ $[M+Na]^+$: 289.11680; found: 289.11641.

Procedure for the transannulation reaction of cyclobutenone 5d: Synthesis of β-lactam 8

A stirred solution of cyclobutenone **5d** (13 mg, 0.05 mmol) and *N*-(4-methoxyphenyl)-1-phenylmethanimine (0.05 mmol) in toluene (1.0 mL) was heated at 150 °C under microwave irradiation for 24 h. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography by using hexanes/ethyl acetate (95:5) as eluent to give compound **8** (13 mg, 53%) as a colorless oil.

(3*RS*,4*SR*)-1,3-Bis(4-methoxyphenyl)-4-phenyl-3-(1-phenylvinyl)-azetidin-2-one 8: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.60$ (m, 2H, 2 CH^{Ar}), 7.28 (m, 2H, 2 CH^{Ar}), 7.13 (m, 2H, 2 CH^{Ar}), 6.97 (m, 3H, 3 CH^{Ar}), 6.80 (m, 4H, 4 CH^{Ar}), 6.33 (m, 2H, 2 CH^{Ar}), 6.01 (d, 1H, $J =$ 0.9 Hz, =C*H*H), 5.61 (s, 1H, CH), 5.44 (d, 1H, $J = 0.9$ Hz, =CH*H*), 3.84 (s, 3H, OCH_3), 3.74 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 166.6$ (C=O), 159.1 (C^{Ar-q}–OCH_3), 156.0 (C^{Ar-q}–OCH_3), 144.3 (C=C), 139.3 (C^{Ar-q}), 134.6 (C^{Ar-q}), 130.8 (C^{Ar-q}), 130.4 (C^{Ar-q}), 128.6 (2 CH^{Ar}), 128.1 (2 CH^{Ar}), 128.0 (CH^{Ar}), 127.9 (2 CH^{Ar}), 127.4 (2 CH^{Ar}), 127.1 (2 CH^{Ar}), 126.6 (CH^{Ar}), 119.1 (=CH_2), 118.8 (2 CH^{Ar}), 114.2 (2 CH^{Ar}), 114.1 (2 CH^{Ar}), 72.4 (C^{Cq}), 65.4 (CH), 55.4 (OCH_3), 55.3 ppm (OCH_3); IR ($CHCl_3$): $\nu = 1746$ (C=O) cm^{-1}; HRMS (ES): calcd for $C_{31}H_{28}NO_3$ $[M+H]^+$: 462.20637; found: 462.20539.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · cyclization · ketones · small ring systems · synthetic methods

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[13] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains compound characterization data, experimental procedures, and copies of NMR spectra for all new compounds.

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Synthetic Methods

Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization versus Rare Bis(cyclization)

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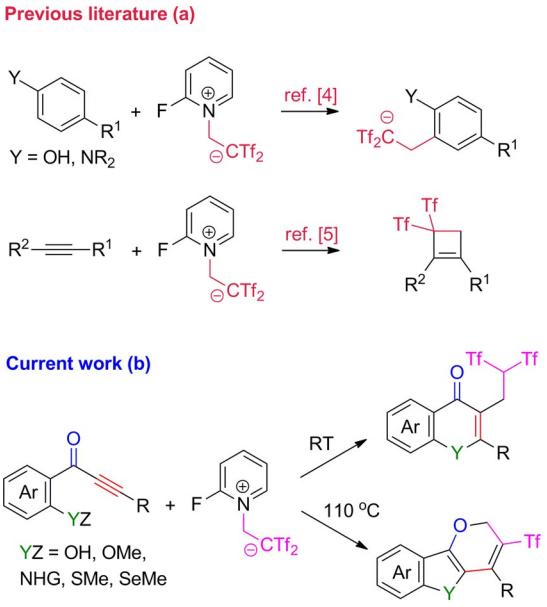
Abstract: Functionalized ynones can be activated by $Tf_2C{=}CH_2$, which was generated in situ, to form zwitterionic species. These species were trapped in an intramolecular fashion by several nucleophiles to generate two major types of triflones in a divergent manner. Through fine-tuning of the reaction temperature, bis(triflyl)-6-membered- or (triflyl)-5-membered-fused-heterocycles were achieved in reasonable yields in a totally selective manner. In this way, bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were constructed. Conceivable mechanistic pathways were suggested on the basis of the isolation of several intermediates and the results from control experiments.

Introduction

Tuning the selectivity in organic synthesis is difficult owing to the usual inherent preference for the creation of a specific type of product. In some cases, a divergent synthesis can be achieved through modification of the promoter, additive, and reagent. Consequently, the discovery of novel strategies for divergent reactions is appealing. Ynones, versatile acetylenic platforms that are readily available from the reaction of acyl chlorides and metal acetylides, have great potential for synthetic applications in nucleophilic additions, cycloadditions, and condensation reactions.[1,2] However, to date, less conventional reactivities are underexplored. The presence of fluoroorganic moieties in organic compounds notably influences the physicochemical[3] and pharmacological properties of the fluorinated derivatives. Particular attention has been paid to the strongly electron-withdrawing triflyl functionality, which exhibits a mild lipophilicity and subsequent improvement in bioavailability. In this context, the group of Yanai has recently developed an innovative methodology that discloses the use of 2-(pyridinium-1-yl)-1,1-bis(perfluoroalkylsulfonyl)ethan-1-ides as a stable source of $Tf_2C{=}CH_2$,[4] whereas we have developed a route for the preparation of bis(triflyl)cyclobutenes[5] (Scheme 1 a). On the basis of these previous observations, we decided to study the reactivity of functionalized ynones. Unexpectedly, divergent reaction paths, with respect to previous results, were encountered. A detailed study of this chemistry unveiled novel aspects of the unique reactivity of ynones, which allowed the direct preparation of various heterocyclic cores that were decorated with fluorinated moieties (Scheme 1 b).



Scheme 1. Background and current design for the synthesis of triflones from 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide.

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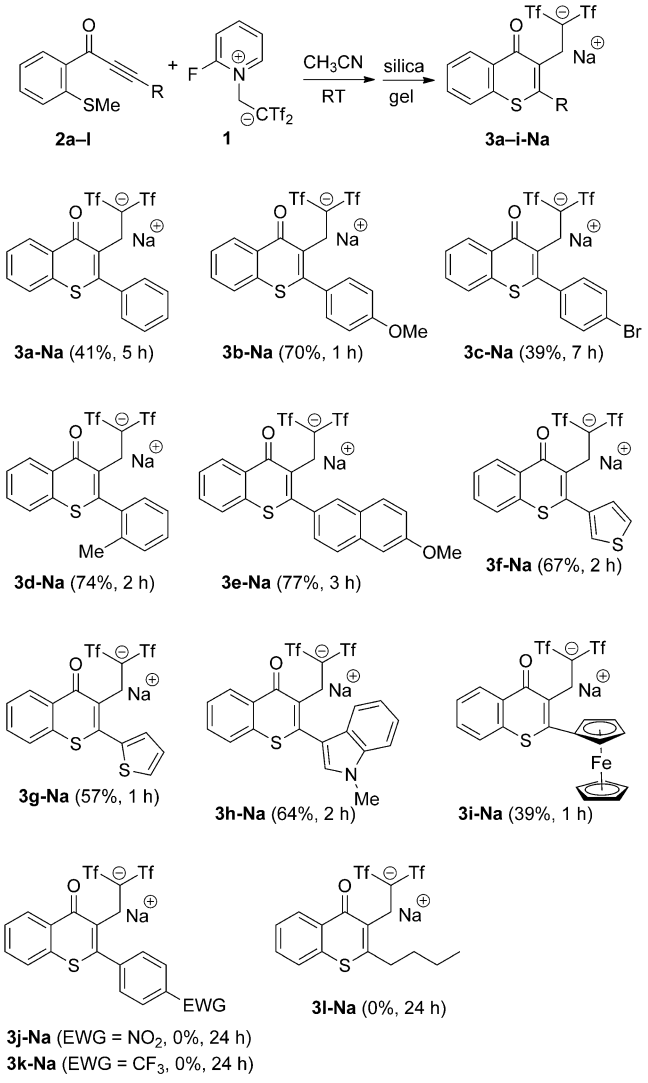
Supporting information and the ORCID identification number(s) for the author(s) of this article are available on the WWW under https://doi.org/10.1002/chem.201800630. It contains experimental procedures as well as full spectroscopic and analytical data for new compounds not included in the Experimental Section.

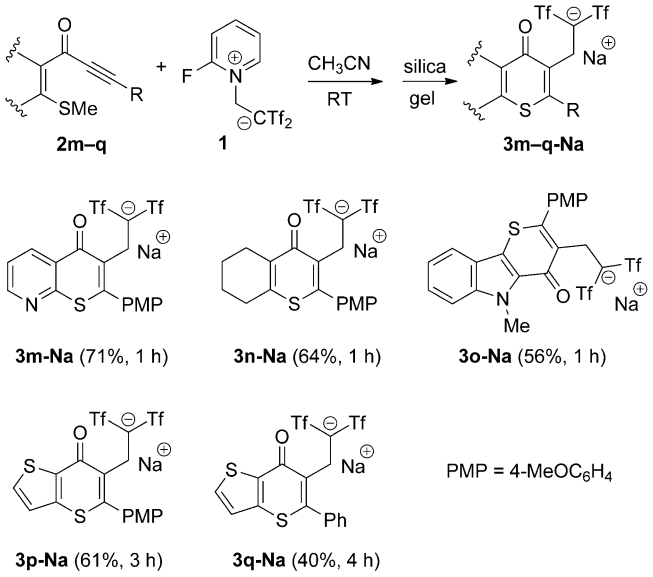
Results and Discussion

To determine the feasibility of using ynones as precursors, 1-[2-(methylthio)phenyl]-3-phenylprop-2-yn-1-one (**2a**)[2a] was treated with 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide (**1**) in acetonitrile at room temperature. Interestingly, the formation of bis(triflyl)thioflavone (**3a**) was observed (Scheme 2) rather than Friedel–Crafts-type bis(triflyl)alkylation or cyclobutene construction (Scheme 1). Notably, a C–S bond,[6] which is present in a vast array of natural products and bioactive molecules, such as thioflavones, was formed under mild conditions. The organofluorine substituent was also incorporated in the same step under metal-free conditions through dual functionalization of the alkyne moiety. With these cyclization conditions in hand, we examined the scope of MeS-functionalized ynones that were susceptible to thioflavone generation. The scope and limitations were initially evaluated through different substitution patterns at the alkyne terminus. Accordingly, various substituents on the aromatic ring at the terminal alkyne, such as methoxy, methyl, and bromo, were well tolerated, and the desired fluorinated thioflavones **3a–d** were isolated in yields of 41 to 77% (Scheme 2). Furthermore, naphthalene-, indole-, thiophene-, and ferrocene-linked alkynes **2e–i** also underwent the thiacyclization/functionalization sequence (Scheme 2). Notably, products **3a–i** easily dissociate the acidic hydrogen atom to provide the corresponding metal salts **3a–i-Na** after column chromatography.[7] Unfortunately, the highly deactivating 4-$NO_2C_6H_4$ and 4-$CF_3C_6H_4$ moieties that were attached to the alkyne group did not afford the corresponding thioflavones **3j** and **k**, and alkynones that bore an alkyl substituent on the alkyne, such as alkyne **2l**, were also inert in the presence of zwitterion **1**.



Scheme 2. Controlled preparation of bis(triflyl)thioflavones **3a–i**.

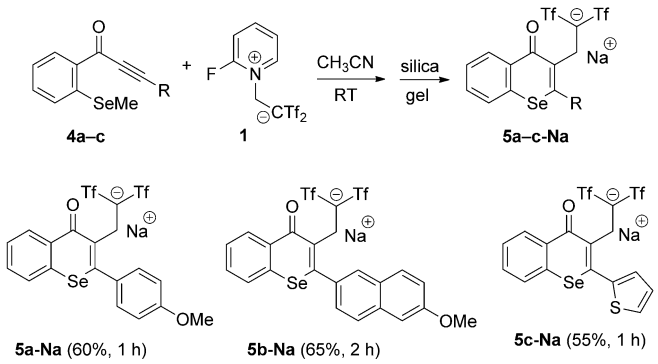
The scope of the reaction was also explored through modification of the MeS–alkynone tether. Variation of the benzene linker was viable, with pyridine-, cyclohexene-, indole-, and thiophene-tethered alkynones all affording the desired organofluorine thioflavones **3m–q** in reasonable yields (Scheme 3).



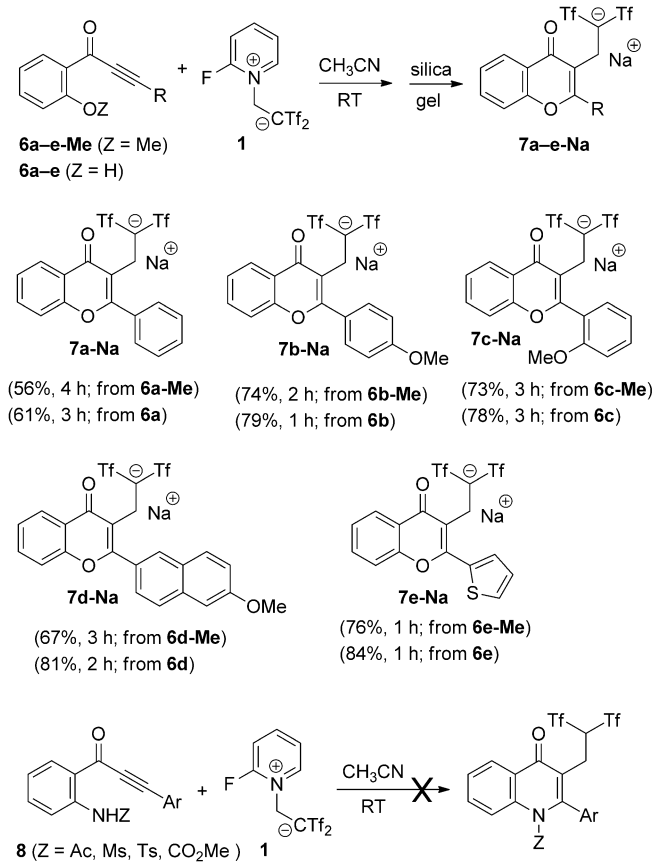
Scheme 3. Controlled preparation of bis(triflyl)thioflavones **3m–q**.

Taking into account the rich chemistry and the important biological properties of organoselenium compounds, the scope of the nucleophile was investigated by replacing the SMe group for an SeMe moiety. Noticeably, the reactions of (methylseleno)-alkynones **4a–c** and zwitterion **1** smoothly gave the desired fluorinated selenoflavones **5a–c** as the exclusive products (Scheme 4).

The nature of the nucleophile could also be modified to oxygen-substituted derivatives. Accordingly, methoxyalkynones **6a–e-Me** and hydroxyalkynones **6a–e** were both found to be suitable cyclization precursors, and bis(triflyl)flavones **7a–e** were accomplished in yields ranging from 56 to 84% (Scheme 5). Unfortunately, the amide functionality in HN–Ac-, HN–Ms-, HN–Ts-, and HN–CO_2Me-substituted amido alkynones **8** was unreactive under the above conditions, which prevented access to fluorinated quinolin-4-one derivatives. Notably, the signal that corresponded to the highly acidic hydrogen on the sulfone alpha-carbon atom (Tf_2CH) was not observed in the



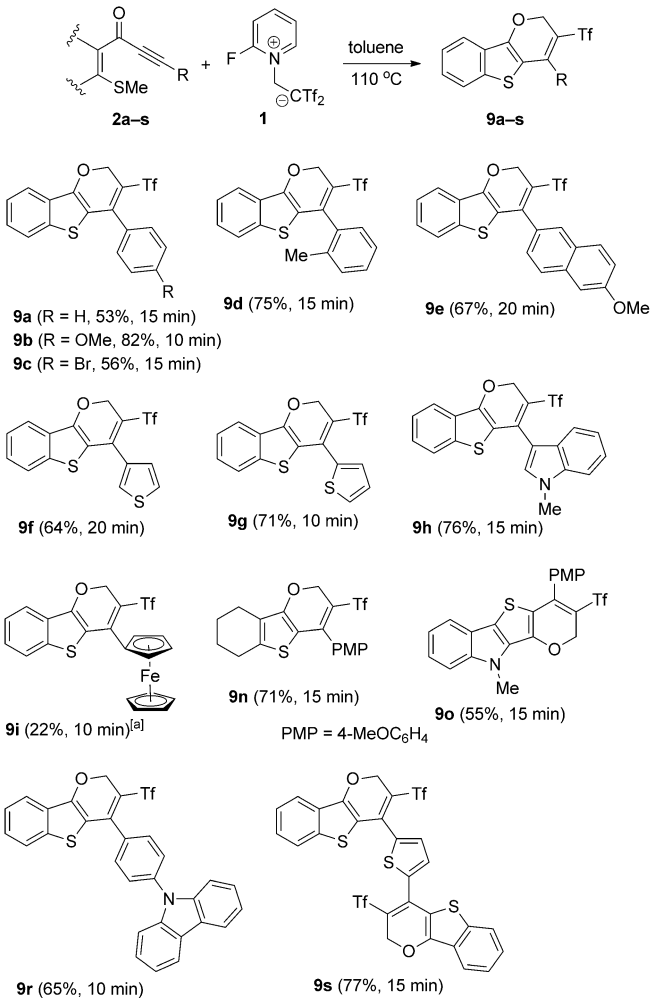
Scheme 4. Controlled preparation of bis(triflyl)selenoflavones **5a–c**.



Scheme 5. Controlled preparation of bis(triflyl)flavones **7a–e**.

^{1}H NMR spectra of compounds **3**, **5**, and **7**, which was attributed to chromatographic purification without re-acidification. Ishihara et al. reported that the purification of strongly acidic compounds by column chromatography on silica gel gives the corresponding calcium salts.[7a] Yanai also reported that Tf_2CH-bearing compounds were strongly acidic and eluted as the corresponding Ca^{2+} salts during silica gel chromatography.[7b] In our case, the metal cation is sodium in accordance with our previous report of a related cyclobutenyl-$[Tf_2CCH_2]^-Na^+$ derivative, which was structurally defined by X-ray crystallographic analysis.[5c] In addition, sodium was detected in representative flavone derivatives, such as **3m-Na**, **5c-Na**, and **7b-Na**, through the use of two different analytical techniques, namely SEM-EDX and ^{23}Na NMR (see the Supporting Information).

Having probed the feasibility of this cyclization/functionalization sequence and tested several structural variations within the acyclic precursors, investigations into a tunable reactivity were initiated by testing variations in the reaction solvent and temperature. Initially, MeS-alkynone **2a** was treated with zwitterion **1** in acetonitrile at 80 °C, which resulted in a mixture (2:1) of bis(triflyl)thioflavone (**3a**) and 3-[(trifluoromethyl)sulfonyl]-2*H*-benzo[4,5]thieno[3,2-*b*]pyran (**9a**). With this promising result in hand, we hoped that fine tuning of the reaction conditions might result in the sole construction of tricycle **9a**. Zwitterion **1** is almost insoluble in apolar or halogenated solvents at RT, but it can be used in these solvents when they are heated at reflux. Replacing acetonitrile with other solvents was found to be useful; to our satisfaction, the addition of zwitterion **1** to a boiling solution of alkynone **2a** in toluene gave the tricycle **9a** exclusively, without any trace of bicycle **3a** (Scheme 6). Noticeably, simple temperature and solvent alterations gave rise to the divergent formation of two entirely distinct fluorinated heterocyclic cores from a common cyclization



Scheme 6. Controlled preparation of tricyclic triflylbenzothienopyrans **9**.
[a] Partial decomposition during chromatographic purification.

precursor. This second domino process allowed the direct metal-free access to a tricyclic framework with the simultaneous formation of C–S, C–O, and C–C bonds. A variety of MeS-alkynones **2** that contained various functional groups and tethers were also submitted to bis(cyclization). As a result, various fused thieno[3,2-*b*]pyrans **9** were achieved with exquisite selectivity in reasonable yields, with the exception of ferrocene derivative **9i**, which was obtained in a reduced yield of 22% (Scheme 6). The reaction was even extended to the symmetrical bis(MeS-alkynone) **2s**, with which a two-fold sequence took place to afford benzothiophene-linked bis(tricycle) **9s** (Scheme 6). To the best of our knowledge, a general access to fused tricyclic benzothienopyrans from acyclic precursors in one synthetic operation has not yet been reported. The structure of tricycle **9a** was confirmed by X-ray crystallography (Figure 1).[8]

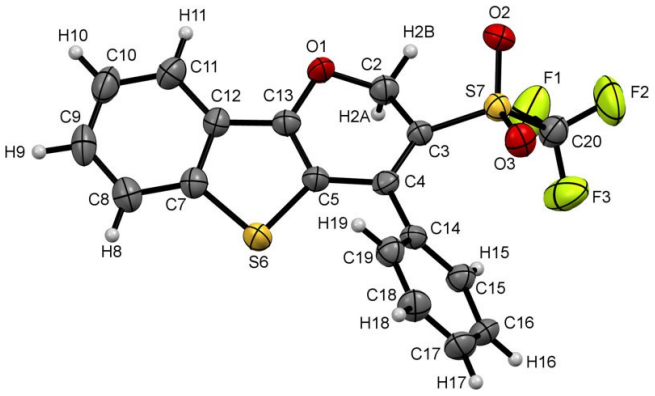
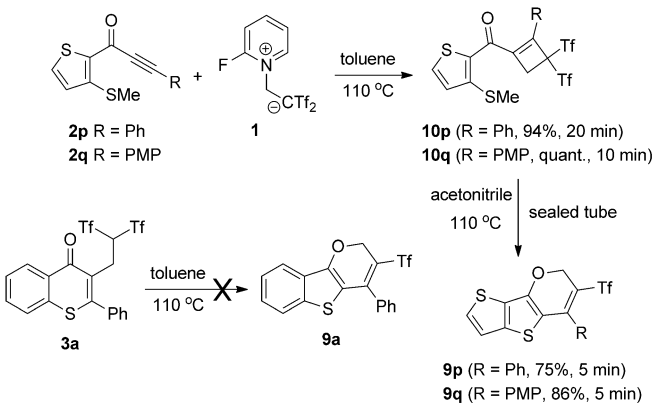
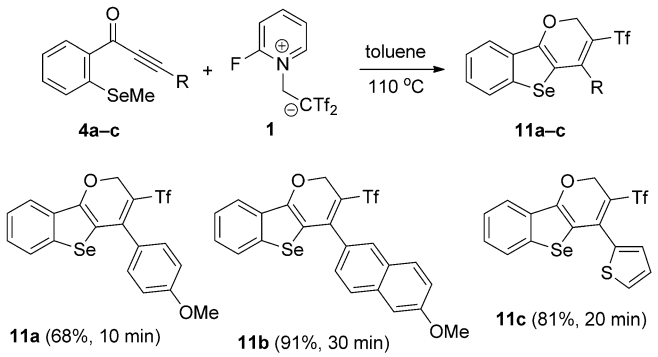


Figure 1. ORTEP drawing of 3-[(trifluoromethyl)sulfonyl]-2*H*-benzo[4,5]thieno[3,2-*b*]pyran **9a**. Thermal ellipsoids shown at 50% probability.



Scheme 7. Controlled preparation of bis(triflyl)cyclobutenes **10p,q** and triflyl(bis-thieno)pyrans **9p,q**.

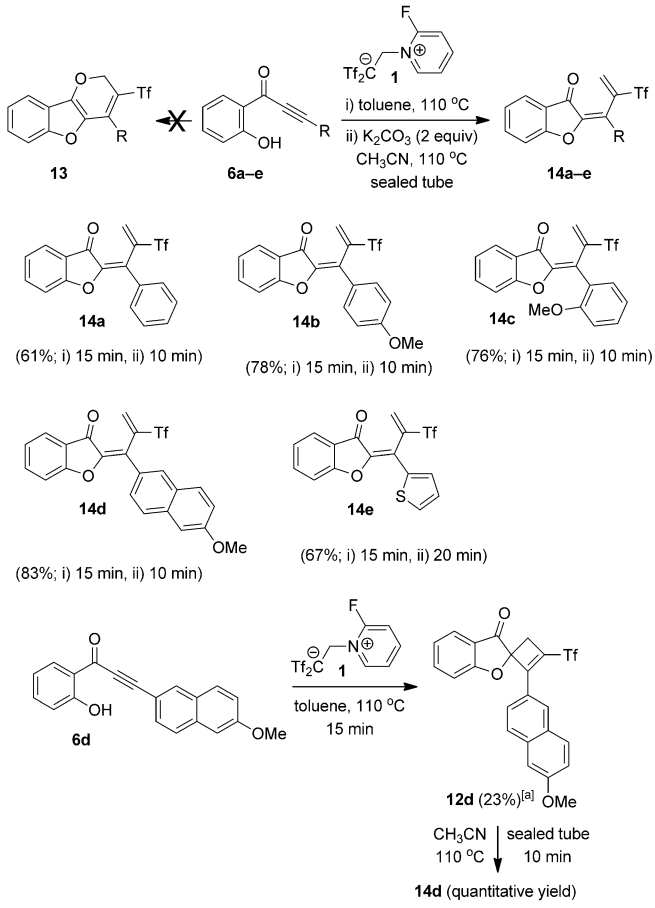


Scheme 8. Preparation of triflylbenzoselenophenopyrans **11**.

We conceived that bicycles of type **3** could be converted into fused tricycles **9** at elevated temperature. However, the treatment of a toluene solution of bicycle **3a** at 110 °C gave no reaction. Even more puzzling was the formation of cyclobutenes **10p** and **q** in almost quantitative yields from thiophene-tethered MeS-alkynones **2p** and **q**, respectively, under the optimized conditions for the formation of tricycles **9**. Fortunately, heating an acetonitrile solution of cyclobutenes **10p** and **q** in a sealed tube at 110 °C resulted in full conversion to 6-(triflyl)-7*H*-thieno[2′,3′:4,5]thieno[3,2-*b*]pyrans **9p** and **q**, respectively (Scheme 7). Therefore, it may be inferred that cyclobutenes **10** and not bicycles **3** are intermediates in the formation reaction of fused pyrans **9**.

It was important to extend the current method for the synthesis of tricyclic thienopyrans to other relevant heterocyclic cores. For example, replacement of the S atom for a bulkier Se normally increases the semiconducting properties of the resultant less aromatic selenophenes in comparison with their thiophene counterparts. We initiated our study by using (methylselanyl)phenyl-propynones **4a–c** as the alkynone partner; gratifyingly, the use of heat did allow the efficient synthesis of 3-(triflyl)-2*H*-benzo[4,5]selenopheno[3,2-*b*]pyrans **11a–c** (Scheme 8). Consequently, MeSe-alkynones were proven to be excellent substrates for the bis(cyclization), because changing the heteroatom from S to Se has no effect on the reactivity pattern of the compound.

The reaction of zwitterion **1** with substrates **6-Me**, which contain a methoxy substituent ortho to the alkynone group, in toluene at 110 °C gave rise to an intractable mixture of products. A beneficial effect was provoked by using hydroxyalkynone substrates **6** instead. The treatment of hydroxyalkynones **6** with zwitterion **1** in boiling toluene did not allow a direct preparation of the expected tricycles; instead, several unstable products were formed. Interestingly, in one case, we were able to isolate a putative intermediate, namely, spirocyclic cyclobutene **12d** (Scheme 9). Fortunately, the reaction of hydroxyalkynones **6** was found to be successful in the presence of a base, which probably enhanced the nucleophilicity of the oxygenated functionality. Among several bases tested, potassium carbonate provided the best results. In this way, hydroxyalkynones **6a–e** suffered a rearrangement reaction to form adducts **14a–e** (Scheme 9). Surprisingly, the expected tricycles **13** were not obtained. Instead, compounds **14** were formed, which bear an open-chain conjugated dienone structure, as confirmed by X-ray diffraction analysis of compound **14e** (Figure 2)[9]. The occurrence of such an unanticipated result could be tentatively explained by bond lengths: the C–S and the C–Se bonds are longer than the C–O bond, which may dis-



Scheme 9. Controlled preparation of triflylallylidenebenzofuranones **14a–e** and spirocyclic cyclobutene **12d**. [a] Partial decomposition during chromatographic purification.

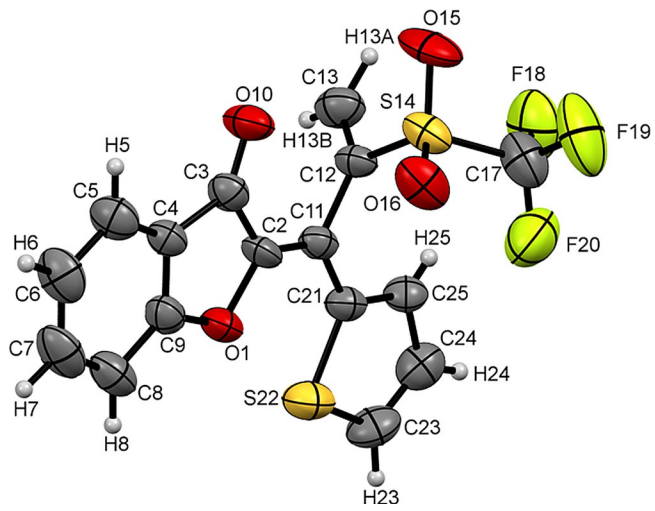
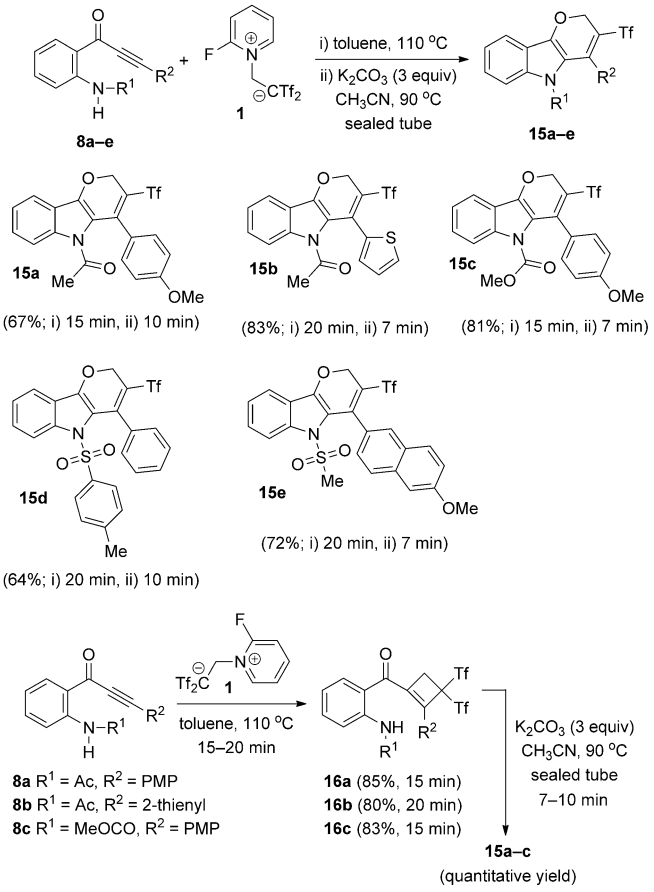


Figure 2. ORTEP drawing of (*E*)-2-(1-(thiophen-2-yl)-2-((trifluoromethyl)sulfonyl)allylidene)benzofuran-3(2*H*)-one **14e**. Thermal ellipsoids shown at 50% probability.

favor the final cyclization in this latter case. Interestingly, adducts **14** are (triflyl)vinyl aurones, a group of flavonoids. When the proposed intermediate **12d** was heated in acetonitrile at 110 °C in a sealed tube, compound **14d** was formed (Scheme 9); this confirmed that spirocyclic cyclobutene species **12** is an intermediate in our cyclization reaction.

Next, we used amido alkynone substrates **8** with the intention of preparing fused indoles. However, no reaction proceeded in the presence of zwitterion **1** at room temperature. Fortunately, under similar conditions to those developed for the preparation of functionalized aurones **14**, various azatricycles **15** were obtained in synthetically valuable yields (Scheme 10).



Scheme 10. Controlled preparation of triflyl-2,5-dihydropyrano[3,2-*b*]indoles **15a–e** and cyclobutenes **16a–c**.

Therefore, both heat and the presence of a base are crucial for the success of the cyclization/rearrangement sequence. The PMP group in product **15a** was be replaced with a naphthyl, thienyl, or phenyl group without attenuation in reaction efficiency. Furthermore, our protocol accommodated different N-protected functional groups, which included acetamides and sulfonamides. The tricyclic structure of 2,5-dihydropyrano[3,2-*b*]indole (**15b**) was confirmed by X-ray diffraction analysis (Figure 3).[10] To obtain direct evidence of a cyclobutene-type intermediate, the reactions between amido alkynones **8a–c** and zwitterion **1** were carried out at 110 °C with suppression of the base treatment. Pleasingly, we isolated cyclobutene derivatives **16a–c** in good yields, and thermal treatment of these strained intermediates in acetonitrile under basic conditions (K_2CO_3) resulted in the formation of tricycles **15a–c**

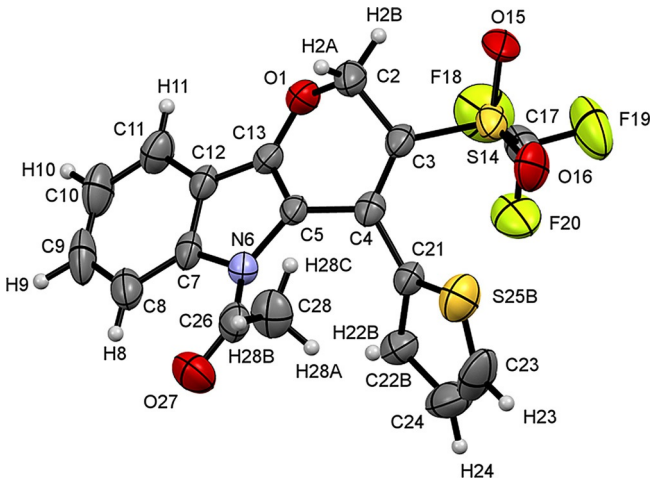


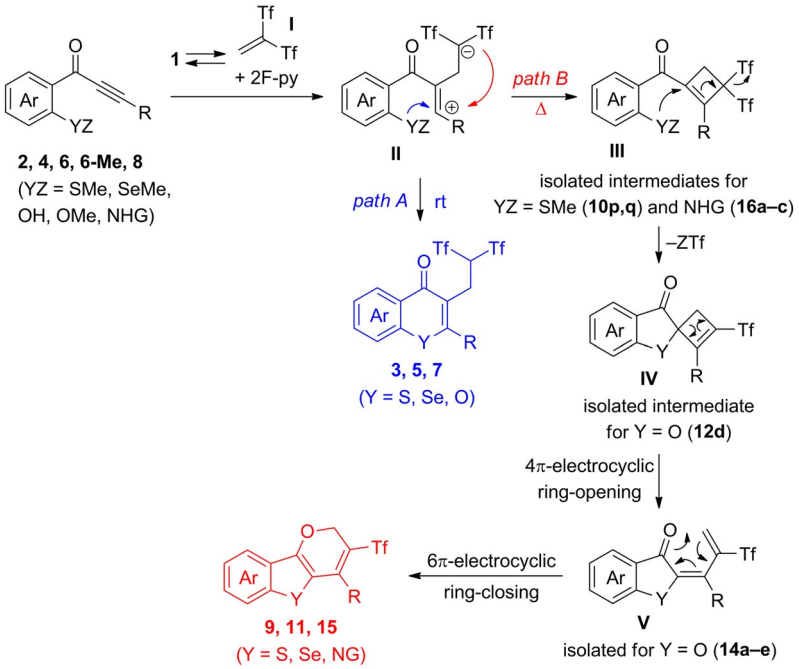
Figure 3. ORTEP drawing of 1-(4-(thiophen-2-yl)-3-((trifluoromethyl)sulfonyl)-pyrano[3,2-*b*]indol-5(2*H*)-yl)ethan-1-onev **15b**. Thermal ellipsoids shown at 50% probability.

(Scheme 10), which suggests that adducts **16** are key intermediates.

A possible pathway for the metal-free formation of bicyclic triflones **3**, **5**, and **7** is outlined in Scheme 11. Formation of 1,1-bis((trifluoromethyl)sulfonyl)ethene (**I**) from 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide (**1**) would trigger a nucleophilic attack of the C2 atom of propynones **2**, **4**, and **6** onto the terminal carbon atom of alkene **I**. The so-formed zwitterionic species **II** would suffer a selective intramolecular heterocyclization to generate bicycles **3**, **5**, and **7** (path A). From common intermediate **II**, we have postulated an alternative path that involves a carbocyclization reaction to generate intermediate cyclobutenes **III** (path B). This alternative cyclobutene formation is not achievable at RT. Subsequently, the regioselective nucleophilic addition of a -SMe, -SeMe, -OH, or -NHP functional group to the C1 atom of bis((trifluoromethyl)-sulfonyl)cyclobut-1-en-1-yl)methanones **III** occurs to form spirocyclic cyclobutene intermediates **IV**. Subsequent rearrangement with cyclobutene ring-opening gives rise to dienone intermediates **V**. Final 6π-electrocyclic ring closure affords tricyclic triflones **9**, **11**, and **15**. This second path must be driven by alleviation of the ring strain linked to the cyclobutene moiety upon formation of the deeply conjugated dienone intermediates **V**. Although the obtainment of cyclobutenes **10p**, **q** (Scheme 7) and **16a–c** (Scheme 10), spirocyclic cyclobutene **12d** (Scheme 9), and dienones **14a–e** (Scheme 9) was serendipitous, these findings are in agreement with the mechanism of Scheme 11, because detectable intermediates were isolated.

Conclusions

We have unveiled the reaction of $Tf_2C{=}CH_2$ with ynones, which gives rise to a divergent preparation of two major triflone-based products. The selectivity of the product can be completely switched through the adjustment of the reaction temperature. In this way, bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were constructed. On the basis of control experiments and the trapping of several intermediates, we have proposed two conceivable reaction mechanisms.



Scheme 11. Rationalization for the formation of bicyclic triflones **3**, **5**, **7** and tricyclic triflones **9**, **11**, **15**.

Experimental Section

General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with a cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra of samples were recorded as $CDCl_3$ solutions, unless otherwise stated. Chemical shifts (δ) are given in ppm relative to TMS (^{1}H, $\delta=0.0$ ppm), $CDCl_3$ (^{1}H, $\delta=7.27$ ppm; ^{13}C, $\delta=76.9$ ppm), C_6D_6 (^{1}H, $\delta=7.16$ ppm; ^{13}C, $\delta=128.0$ ppm), [D_6]acetone (^{1}H, $\delta=2.05$ ppm; ^{13}C, $\delta=206.3$ ppm), or CD_3CN (^{1}H, $\delta=1.94$ ppm; ^{13}C, $\delta=118.2$ ppm). Low and high resolution mass spectra were recorded on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer by using the electronic impact (EI) or electrospray (ES) modes, unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD diffractometer by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. All commercially available compounds were used without further purification.

General procedure for the reaction between alkynones 2a–q, 4a–c, 6a–e, and 6a–e-Me with pyridinium salt 1 at room temperature: Preparation of bis(triflyl)thioflavones 3a–i, 3m–q, bis(triflyl)selenoflavones 5a–c, and bis(triflyl)flavones 7a–e

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide (**1**, 0.2 mmol) was added at RT to a solution of the appropriate alkynone **2a–q**, **4a–c**, **6a–e**, or **6a–e-Me** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at RT until disappearance of the starting material was visualized by TLC, and the mixture was concentrated under reduced pressure. Column chromatography (hexanes/ethyl acetate) of the residue followed by further dissolving in Et_2O, precipitation with hexanes, and filtration gave analytically pure compounds. Spectroscopic and analytical data for adducts **3a–i-Na**, **3m–q-Na**, **5a–c**, and **7a–e-Na** follow.

Bis(trifluoromethylsulfonyl)thioflavone 3b: Alkynone **2b** (40 mg, 0.14 mmol), after flash chromatography of the residue (hexanes/ethyl acetate, 1:1) with further dissolving in Et_2O and precipitation with hexanes, gave compound **3b-Na** (57 mg, 70%) as a colorless solid; m.p. 219–221 °C; ^{1}H NMR (300 MHz, CD_3CN, 25 °C): $\delta=8.51$ (m, 1H, CH^{Ar}), 7.73 (m, 2H, $2CH^{Ar}$), 7.60 (m, 1H, CH^{Ar}), 7.32 (m, 2H, $2CH^{Ar}$), 7.04 (m, 2H, $2CH^{Ar}$), 3.90 (s, 3H, OCH_3), 3.67 ppm (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 °C): $\delta=181.3$ (C=O), 161.4 (C^{Ar-q}-OMe), 152.1 (S-*C*=*C*), 138.3 (C^{Ar-q}), 132.4 (CH^{Ar}), 132.2 (S-C=C), 131.8 ($2CH^{Ar}$), 131.5 (C^{Ar-q}), 129.6 (C^{Ar-q}), 129.4 (CH^{Ar}), 128.2 (CH^{Ar}), 126.4 (CH^{Ar}), 122.0 (q, $J_{CF}=328.9$ Hz, $2CF_3$), 114.3 ($2CH^{Ar}$), 63.5 (CTf_2), 55.9 (OCH_3), 27.6 ppm (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 °C): $\delta=-80.4$ ppm (s, 6F, $2CF_3$); IR (CH_3CN): $\tilde{\nu}=1723$ (C=O), 1379, 1110 (O=S=O), 1215 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{20}H_{15}F_6O_6S_3$: 560.99295 $[M+H]^+$; found: 560.99056.

Bis(trifluoromethylsulfonyl)selenoflavone 5b: Alkynone **4b** (30 mg, 0.079 mmol), after flash chromatography (hexanes/ethyl acetate, 1:1) with further dissolving in Et_2O and precipitation with hexanes, gave compound **5b-Na** (35 mg, 65%) as a colorless solid; m.p. 196–198 °C; ^{1}H NMR (500 MHz, [D_6]acetone, 25 °C): $\delta=8.50$ (dd, 1H, $J=8.1$, 1.3 Hz, CH^{Ar}), 7.86 (s, 1H, CH^{Ar}), 7.81 (m, 2H, $2CH^{Ar}$), 7.76 (d, 1H, $J=7.9$ Hz, CH^{Ar}), 7.57 (m, 1H, CH^{Ar}), 7.46 (m, 2H, $2CH^{Ar}$), 7.31 (d, 1H, $J=2.4$ Hz, CH^{Ar}), 7.16 (dd, 1H, $J=8.9$, 2.6 Hz, CH^{Ar}), 3.90 (s, 3H, OCH_3), 3.76 ppm (s, 2H, CH_2); ^{13}C NMR (125 MHz, [D_6]acetone, 25 °C): $\delta=183.5$ (C=O), 159.7 (C^{Ar-q}-OMe), 151.8 (S-*C*=*C*), 137.7 (C^{Ar-q}), 135.8 (C^{Ar-q}), 135.0 (S-C=C), 134.5 (C^{Ar-q}), 133.6 (C^{Ar-q}), 132.2 (CH^{Ar}), 131.5 (CH^{Ar}), 130.9 (CH^{Ar}), 129.2 (C^{Ar-q}), 129.2 (CH^{Ar}), 128.5 (CH^{Ar}), 128.1 ($2CH^{Ar}$), 127.5 (CH^{Ar}), 122.4 (q, $J_{CF}=329.7$ Hz, $2CF_3$), 120.4 (CH^{Ar}), 106.8 (CH^{Ar}), 64.2 (CTf_2), 55.9 (OCH_3), 28.8 ppm (CH_2); ^{19}F NMR (282 MHz, [D_6]acetone, 25 °C): $\delta=-79.8$ ppm (s, 6F, $2CF_3$); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): $\delta=400.3$ ppm (s, 1Se, Se); IR (acetone): $\tilde{\nu}=1726$ (C=O), 1371, 1110 (O=S=O), 1211 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{24}H_{17}F_6O_6S_2Se$: 658.95308 $[M+H]^+$; found: 658.95286.

Bis(trifluoromethylsulfonyl)flavone 7b: Alkynone **6b** (20 mg, 0.08 mmol), after flash chromatography (hexanes/ethyl acetate, 1:1) with further dissolving in Et_2O and precipitation with hexanes, gave compound **7b-Na** (36 mg, 79%) as a colorless solid; m.p. 223–225 °C; ^{1}H NMR (300 MHz, CD_3CN, 25 °C): $\delta=8.22$ (dd, 1H, $J=8.0$, 1.5 Hz, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 7.57 (d, 1H, $J=8.0$ Hz, CH^{Ar}), 7.46 (m, 3H, $3CH^{Ar}$), 7.06 (m, 2H, $2CH^{Ar}$), 3.91 (s, 3H, OCH_3), 3.67 ppm (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3CN, 25 °C): $\delta=179.7$ (C=O), 165.2 (O-*C*=*C*), 162.0 (C^{Ar-q}-OMe), 156.8 (C^{Ar-q}-O), 134.7 (CH^{Ar}), 132.0 ($2CH^{Ar}$), 126.5 (C^{Ar-q}), 126.1 (CH^{Ar}), 125.7 (CH^{Ar}), 123.6 (C^{Ar-q}), 121.9 (q, $J_{CF}=328.3$ Hz, $2CF_3$), 119.4 (O-C=C), 118.8 (CH^{Ar}), 114.2 ($2CH^{Ar}$), 63.4 (CTf_2), 56.0 (OCH_3), 25.4 ppm (CH_2); ^{19}F NMR (282 MHz, CD_3CN, 25 °C): $\delta=-80.5$ ppm (s, 6F, $2CF_3$); IR (CH_3CN): $\tilde{\nu}=1719$ (C=O), 1376, 1109 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{20}H_{15}F_6O_7S_2$: 545.01579 $[M+H]^+$; found: 545.01488.

General procedure for the reaction between alkynones 2a–i, 2n–s, and 4a–c with pyridinium salt 1 at 110 °C: Preparation of triflylbenzothienopyrans 9a–i, 9n–s, and triflylbenzoselenophenopyrans 11a–c

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide (**1**, 0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone **2a–i**, **2n–s**, or **4a–c** (0.2 mmol) in toluene (4 mL) heated at reflux. The reaction was stirred at 110 °C until disappearance of the starting material was visualized by TLC, and the mixture was concentrated under reduced pressure. Adducts **2p** and **q** required additional heating in acetonitrile in a sealed tube at 110 °C, because after the initial heating in toluene, cyclobutenes **10p** and **q** were isolated. Column chromatography (hexanes/ethyl acetate or hexanes/toluene) of the residue gave analytically pure compounds. Spectroscopic and analytical data for adducts **9a–i**, **9n–s**, and **4a–c** follow.

Triflylbenzothienopyran 9b: Alkynone **2b** (40 mg, 0.14 mmol), after flash chromatography (hexanes/ethyl acetate, 97:3), gave compound **9b** (49 mg, 82%) as a yellow solid; m.p. 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.89$ (m, 1H, CH^{Ar}), 7.71 (m, 1H, CH^{Ar}), 7.47 (m, 2H, $2CH^{Ar}$), 7.33 (m, 2H, $2CH^{Ar}$), 6.98 (m, 2H, $2CH^{Ar}$), 5.37 (s, 2H, OCH_2), 3.88 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=161.0$ (C^{Ar-q}-OMe), 155.3 (C^{Ar-q}), 154.9 (C^{Ar-q}), 142.2 (C^{Ar-q}), 130.4 ($2CH^{Ar}$), 128.9 (CH^{Ar}), 128.5 (C^{Ar-q}), 125.5 (C^{Ar-q}), 125.2 (CH^{Ar}), 123.3 (CH^{Ar}), 122.9 (CH^{Ar}), 120.0 (q, $J_{CF}=326.8$ Hz, CF_3), 119.9 (*C*=*C*-Tf), 113.2 (CH^{Ar}), 105.0 (C=C-Tf), 67.4 (OCH_2), 55.3 ppm (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-79.0$ ppm (s, 3F, CF_3); IR ($CHCl_3$): $\tilde{\nu}=1379$, 1110 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{19}H_{14}F_3O_4S_2$: 427.02801 $[M+H]^+$; found: 427.02737.

Triflylbenzoselenophenopyran 11b: Alkynone **4b** (30 mg, 0.079 mmol), after flash chromatography (hexanes/ethyl acetate, 95:5), gave compound **11b** (39 mg, 91%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.94$ (m, 1H, CH^{Ar}), 7.78 (m, 4H, $4CH^{Ar}$), 7.45 (m, 3H, $3CH^{Ar}$), 7.22 (m, 2H, $2CH^{Ar}$), 5.44 (d, 1H, $J=12.7$ Hz, OC*H*H), 5.38 (d, 1H, $J=12.7$ Hz, OCH*H*), 3.96 ppm (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=158.8$ (C^{Ar-q}-OMe), 156.8 (C^{Ar-q}),

156.4 (C^{Ar-q}), 142.7 (C^{Ar-q}), 135.1 (C^{Ar-q}), 131.3 (C^{Ar-q}), 130.3 (C^{Ar-q}), 130.0 (CH^{Ar}), 129.0 (CH^{Ar}), 127.9 (CH^{Ar}), 127.7 (C^{Ar-q}), 126.3 (CH^{Ar}), 126.2 (CH^{Ar}), 126.1 (CH^{Ar}), 125.6 (CH^{Ar}), 125.0 (CH^{Ar}), 120.1 (q, J_{CF} = 326.9 Hz, CF_3), 119.9 (C=C-Tf), 119.7 (CH^{Ar}), 105.8 (CH^{Ar}), 105.6 (C=C-Tf), 67.0 (OCH_2), 55.4 ppm (OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −78.9 ppm (s, 3F, CF_3); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 441.7 ppm (s, 1Se, Se); IR ($CHCl_3$): $\tilde{\nu}$ = 1371, 1109 (O=S=O), 1210 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{23}H_{16}F_3O_4SSe$: 524.98819 $[M+H]^+$; found: 524.98730.

General procedure for the reaction between alkynones 6a–e and pyridinium salt 1 at 110 °C: Preparation of triflylallylidenebenzofuranones 14a–e

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide (**1**, 0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone **6a–e** (0.2 mmol) in toluene (4 mL) at reflux. The reaction was stirred at 110 °C until disappearance of the starting material was visualized by TLC, and the mixture was concentrated under reduced pressure. K_2CO_3 (2 equiv) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL). The resulting mixture was heated at 110 °C (typically 15 min) in a sealed tube. The reaction was allowed to cool to RT, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/hexanes). Spectroscopic and analytical data for adducts **14a–e** follow. After the first reaction step, spirocyclic cyclobutene **12d** was isolated and fully characterized.

Triflylallylidenebenzofuranone 14b: Alkynone **6b** (20 mg, 0.08 mmol), after flash chromatography (hexanes/ethyl acetate, 8:2), gave compound **14b** (25 mg, 78%) as a yellow solid; m.p. 178–180 °C; ^{1}H NMR (700 MHz, $Cl_2DC/CDCl_2$, 60 °C): δ = 7.79 (d, 1H, J = 7.5 Hz, CH^{Ar}), 7.70 (m, 3H, 3CH^{Ar}), 7.35 (d, 1H, J = 8.3 Hz, CH^{Ar}), 7.29 (t, 1H, J = 7.4 Hz, CH^{Ar}), 7.05 (m, 2H, 2CH^{Ar}), 6.74 (s, 2H, =CH_2), 3.91 ppm (s, 3H, OCH_3); ^{13}C NMR (175 MHz, $Cl_2DC/CDCl_2$, 60 °C): δ = 164.6 (C^{Ar-q}-O), 161.2 (C^{Ar-q}-OMe), 145.2 (C^{Ar-q}), 136.8 (CH^{Ar}), 131.9 (2CH^{Ar}), 124.6 (C^{Ar-q}), 124.1 (CH^{Ar}), 123.9 (CH^{Ar}), 121.5 (C=C), 119.8 (q, J_{CF} = 328.1 Hz, CF_3), 114.4 (2CH^{Ar}), 113.0 (CH^{Ar}), 99.6 (C-Tf), 55.6 ppm (OCH_3); ^{19}F NMR (282 MHz, $Cl_2DC/CDCl_2$, 25 °C): δ = −75.3 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1703 (C=O), 1365, 1106 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{19}H_{14}F_3O_5S$: 411.05086 $[M+H]^+$; found: 411.05121.

General procedure for the reaction between alkynones 8a–e and pyridinium salt 1 at 110 °C: Preparation of triflyl-2,5-dihydropyrano[3,2-*b*]indoles 15a–e

2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 (0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone **8a–e** (0.2 mmol) in toluene (4 mL) at reflux. The reaction was stirred at 110 °C until disappearance of the starting material was visualized by TLC, and the mixture was concentrated under reduced pressure. K_2CO_3 (3 equiv) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL), and the resulting mixture was heated at 90 °C (typically 15 min) in a sealed tube. The reaction was allowed to cool to RT, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/hexanes). Spectroscopic and analytical data for adducts **15a–e** follow. After the first reaction step, cyclobutenes **16a–c** were isolated and fully characterized.

Triflyl-2,5-dihydropyrano[3,2-*b*]indole 15b: Alkynone **8b** (35 mg, 0.06 mmol), and after flash chromatography (hexanes/ethyl acetate, 9:1→8:2) gave compound **15b** (22 mg, 83%) as a yellow solid; m.p. 152–154 °C; ^{1}H NMR (700 MHz, $CDCl_3$, 50 °C): δ = 8.34 (d, 1H, J = 8.6 Hz, CH^{Ar}), 7.78 (d, 1H, J = 7.9 Hz, CH^{Ar}), 7.67 (d, 1H, J = 5.0 Hz, CH^{Ar}), 7.64 (t, 1H, J = 7.6 Hz, CH^{Ar}), 7.52 (d, 1H, J = 1.9 Hz, CH^{Ar}), 7.40 (t, 1H, J = 7.6 Hz, CH^{Ar}), 7.17 (dd, 1H, J = 4.9, 3.4 Hz, CH^{Ar}), 5.35 (s, 2H, OCH_2), 1.91 ppm (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$, 50 °C): δ = 170.0 (NC=O), 156.9 (C^{Ar-q}), 155.8 (C^{Ar-q}), 142.2 (C^{Ar-q}), 135.1 (CH^{Ar}), 132.5 (CH^{Ar}), 131.7 (CH^{Ar}), 127.3 (CH^{Ar}), 124.7 (CH^{Ar}), 122.6 (C=C-Tf), 120.9 (CH^{Ar}), 120.3 (q, J_{CF} = 327.2 Hz, CF_3), 117.7 (C^{Ar-q}), 116.8 (CH^{Ar}), 100.1 (C=C-Tf), 69.6 (OCH_2), 25.5 ppm (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −78.5 ppm (s, 3F, CF_3); IR ($CHCl_3$): $\tilde{\nu}$ = 1665 (C=O), 1362, 1108 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): *m/z* calcd for $C_{18}H_{13}F_3NO_4S_2$: 428.02326 $[M+H]^+$; found: 428.02427.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · cyclization · fluorine · heterocycles · synthetic methods

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[8] CCDC 1528521 (**9a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[9] CCDC 1815354 (**14e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] CCDC 1817363 (**15b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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CHEMISTRY AN ASIAN JOURNAL Full Paper

Structure Elucidation

Synthesis and Characterization of Stable Phosphorus Carbabetaines

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Abstract: Phosphorus 1,3- and 1,4-carbabetaines with 'P(+)–C–C(–)' and 'P(+)–C–C–C(–)' structures, respectively, in which the carbanion moiety was significantly stabilized by two trifluoromethylsulfonyl groups, have been synthesized and characterized. Analysis of their X-ray crystal structures revealed that any attractive interactions between the anionic and cationic moieties were negligibly weak. This result was corroborated by using natural bond orbital (NBO) and Bader's quantum theory of atoms in molecules (QTAIM) models. In contrast, performing the same analysis of a known 1,3-carbabetaine equivalent, which can be drawn as a 'P(+)–C–C=C–O(–)' resonance structure, revealed pronounced charge-transfer interactions between the anionic and cationic moieties.

1. Introduction

Phosphorus betaines are an important class of compounds in terms of their structure, properties, and reactivity.[1] Throughout the history of the Wittig reaction, 1,4-phosphonium oxides (1,4-oxabetaines),[2] which have a 'P^+–C–C–O^-' structure,[3] have been the subject of fierce discussion, because only four-membered oxaphosphetanes have been detected in a Wittig reaction mixture by using NMR spectroscopy.[4] Free 1,4-oxabetaines are highly unstable and, to the best of our knowledge, have only been isolated once, by Ionkin et al. in 2007.[5,6] In contrast, there have been a number of reports of the isolation of thiolate analogues, because the P–S bond is thermodynamically weaker than the P–O bond.[1] In this context, 1,3- and 1,4-phosphonium alkanides (carbabetaines), which have 'P^+–C–C^-' and 'P^+–C–C–C^-' structures, respectively, are particularly interesting. Some structural equivalents, as exemplified by compounds **1**[7,8] and **2**,[9] have been isolated (Figure 1). However,

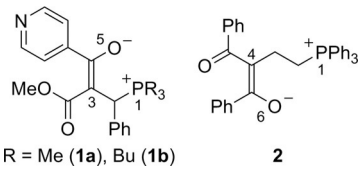

Figure 1. Structures of previously reported carbabetaine equivalents.

in both cases, the "enolate" resonance structure contributes more to the anionic moiety than the "acylcarbanion" resonance structure. Therefore, these compounds should be considered as a type of oxabetaine, rather than as carbabetaines. Such 1,5-oxabetaines have also been regarded as generally unstable, because they undergo rapid ring-closure and afford pentavalent 1,2-oxaphospholenes. In fact, a number of such five-membered compounds have been characterized.[10] In the case of compound **1**, the betaine structure was determined by using single-crystal X-ray diffraction data; however, its geometry still implied the presence of some interactions between the anionic oxygen atom and the cationic phosphorus atom. On the other hand, the crystallographic structure of 1,6-oxabetaine **2** has not yet been reported in the literature.

We are interested in the synthesis of zwitterions that contain a highly stabilized $[Tf_2C]^-$ moiety and their application as synthetic reagents and catalysts.[11] Recently, we found that 2-fluoropyridinium salt **3** was an effective reagent for the in situ generation of highly electrophilic 1,1-bis(trifluoromethylsulfonyl)-ethylene (**4**; Scheme 1) and was successfully applied to the synthesis of a superacidic carbon acid, denoted as Tf_2CHR.[12]

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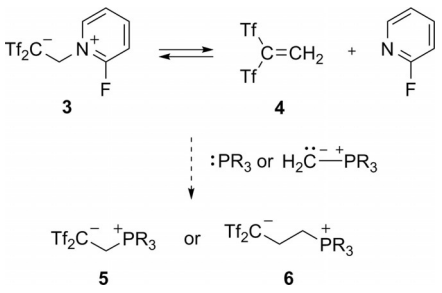
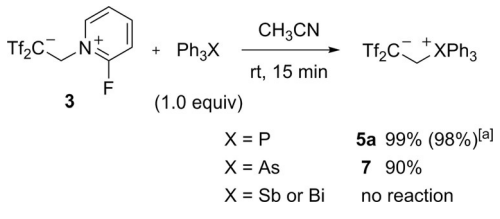


Scheme 1. In situ generation of $Tf_2C{=}CH_2$ (**4**) and this work. Tf = trifluoromethylsulfonyl.

Cycloaddition reactions of in-situ-generated compound **4** with 1,3-dienes,[12b,13] alkynes,[14] and organic azides[15] also proceeded smoothly to produce the corresponding triflones. Although 2-fluoropyridinium salt **3** rapidly formed an equilibrium mixture of compound **4** and 2-fluoropyridine in MeCN, the reagent itself is a shelf-stable and easy-to-handle crystalline solid. In this context, we were interested in the reactions of compound **3** with phosphorus-containing nucleophiles. Herein, we report the synthesis of 1,3- and 1,4-carbabetaines through the reaction of salt **3** with phosphines or phosphonium ylides. Our phosphorus betaines, $R_3P^+{-}(C)_n{-}[CTf_2]^-$ ($n = 1$, 2), were easily isolable and stable, and could be considered as the more-pronounced carbabetaines. Research achievements with Tf_2CHR compounds have stimulated the development of new organocatalysts that contain Tf_2CH groups as a strongly acidic functionality.[16,17] In such catalytic systems, it has been proposed that bulky and chemically inert $[Tf_2CR]^-$ groups endow cationic reaction intermediates with extremely high electrophilicity. This work will also provide fundamental insight into such catalytic systems.

2. Results and Discussion

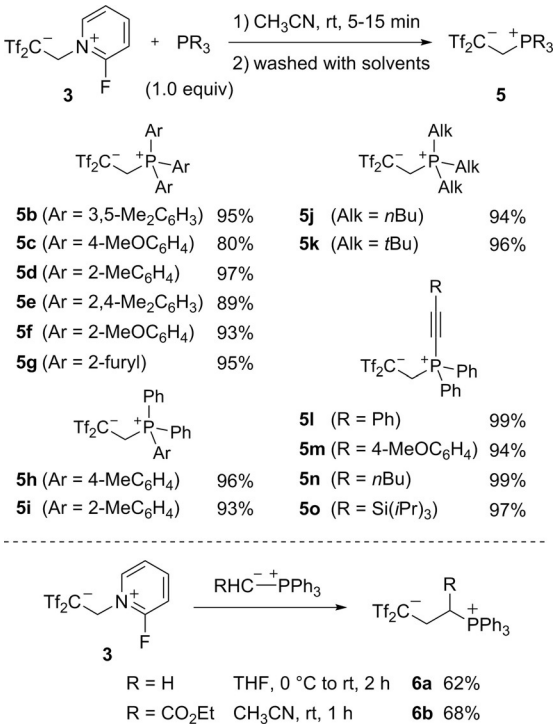
First, we examined the reactions of 2-fluoropyridinium salt **3** with Ph_3P and Ph_3As as Group 15 nucleophiles (Scheme 2). When compound **3** was treated with 1.0 equivalent of Ph_3P in MeCN, the reaction was complete within 15 minutes at room temperature to form the desired *P*-alkylation product (**5a**), which was isolated in 99% yield by washing the crude material with CH_2Cl_2. Likewise, Ph_3As was converted into the corresponding betaine (**7**) in 90% yield. In contrast, reactions with Sb and Bi analogues did not give any products, even on heating at reflux. Two other methods for the generation of compound **4** have been reported: a retro-Michael reaction of



Scheme 2. Reactions of 2-fluoropyridinium salt **3** with Ph_3P, Ph_3As, Ph_3Sb, and Ph_3Bi. [a] The yield of compound **5a** from the reaction with $Tf_2CHCH_2CHTf_2$ is given in parentheses.

$Tf_2CHCH_2CHTf_2$[18] and a self-promoted condensation reaction of Tf_2CH_2 with formaldehyde.[13] Under the former set of conditions, compound **5a** was formed in 98% yield, whereas no product formation was observed under the latter set of conditions. Notably, compound **5a** was stable and thermal decomposition in boiling toluene was not observed.

Under similar conditions, we performed the reactions of 2-fluoropyridinium salt **3** with a range of phosphines (Scheme 3). Triarylphosphines, including derivatives that contained a bulky 2-substituted phenyl group(s), gave the corresponding *P*-alkylated products (**5b**–**5i**) in excellent yields. Likewise, trialkylphosphonium products **5j** and **5k** were obtained from the reactions of salt **3** with nBu_3P and tBu_3P, respectively. Sterically less-hindered alkynyldiphenylphoshines were also converted into the desired products (**5l**–**5o**), with aryl, alkyl, and trialkylsilyl substituents on the C(sp) atom. Notably, in these cases, the [2+2] cycloaddition products were not formed.[14a,b] In contrast, in-situ-generated compound **4** did not form any adducts during the reactions with some sulfides. To obtain structurally related 1,4-carbabetaines, we examined the reactions with phosphorus ylides. Upon treatment of salt **3** with an unstabilized ylide that was derived from methyltriphenylphosphonium bromide and *n*BuLi, the desired adduct (**6a**) was obtained in 62% yield. Likewise, a stabilized ylide was converted into adduct **6b**. The ^{31}P NMR chemical shift of tributylphosphonium **5j** ($\delta = 33.1$ ppm) was very close to that of previously reported betaine **1b** ($\delta = 32.3$ ppm).[7] ^{13}C NMR analysis of compounds **5** and **6** revealed the presence of anionic carbon atoms as singlets at $\delta = 55.5$–60.5 and 62.9–63.1 ppm, respectively. These data suggested that all of the products could be considered as



Scheme 3. Synthesis of 1,3-carbabetaine **5** and 1,4-carbabetaine **6**. Yields of isolated compounds are reported.

pronounced carbabetaines, as further evidenced by experimental and theoretical analyses of selected compounds (see below).

We performed X-ray crystallographic analysis of nine compounds: 1,3-carbabetaines **5a**, **5e**, **5f**, **5i**, **5l**, **5m**, and **7**; and 1,4-carbabetaines **6a** and **6b**. The structures of compounds **5a**, **5i**, and **6a** are shown as representative examples in Figure 2 and their key parameters are summarized in Table 1 (for the other compounds, see the Supporting Information). In all cases, a planar geometry of the anionic C1 atom and a tetrahedral structure of the cationic P1 atom were observed, which suggested that any direct interatomic interaction between the C1 and P1 atoms was negligibly weak, at least in the crystalline environment. In particular, in 1,4-carbabetaines **6a** and **6b**, an antiperiplanar orientation around the C2–C3 bond would make any intramolecular interactions ineffective. The stereochemistry of the two CF_3 groups relative to the plane of the C1 atom was another interesting structural feature: the two CF_3 groups adopted an *anti* conformation in compounds **5a**, **5l**, **5m**, and **6b**, but adopted a *syn* conformation in compounds **5e**, **5f**, **5i**, **6a**, and **7**. Similar to our previous work,[11,12a] the interatomic distances between the C1 atom and the S1/S2 atoms in all of the structures were notably shorter than the S–C(F_3) distances. This conformational behavior of the two CF_3 groups and the bond lengths in the $[Tf_2C]^-$ group confirmed delocalization of the electron lone pairs on the C1 atom to the $\sigma^*_{S-C(F_3)}$ orbitals, which is known as negative hyperconjugation.

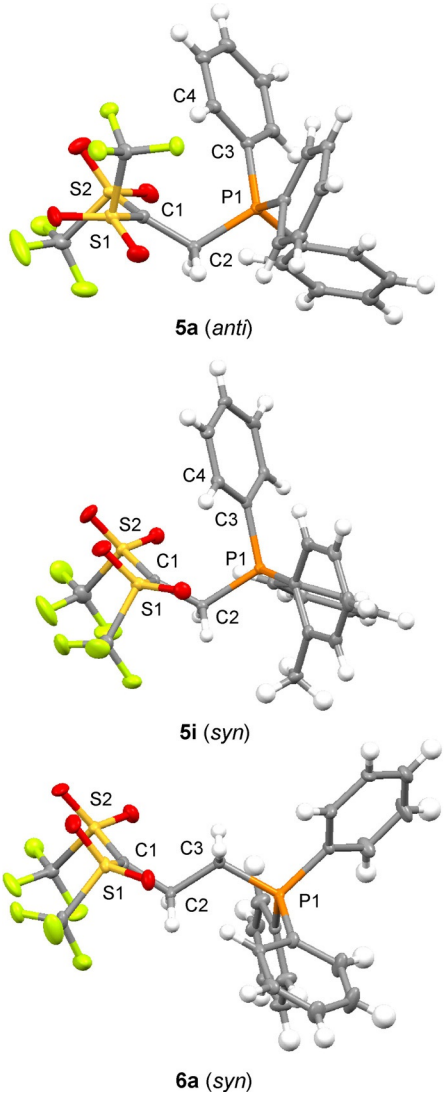


Figure 2. Crystallographic structures of compounds **5a**, **5i**, and **6a**; thermal ellipsoids are set at 50% probability.

Table 1. Interatomic distances and angles in compounds **5a**, **5i**, and **6a**, based on X-ray crystallographic analysis and DFT calculations.

Compound		C1–C2 [pm]	C2–P1 [pm]	C1–S [pm][a]	S–C(F_3) [pm][b]	C1–C2–P1 [°]
5a	expt.	150.9(4)	184.6(3)	168.6(3) 168.7(3)	185.6(3) 185.7(4)	117.2(2)
	calcd	149.2	185.1	169.5 170.6	186.3 187.2	115.2
5i	expt.	150.5(3)	185.3(2)	164.5(2) 168.3(2)	184.6(2) 184.4(2)	117.6(1)
	calcd	149.1	187.5	169.1 170.1	186.5 186.1	114.1
6a	exp.	152.5(6)	181.0(5)[c]	168.1(5) 167.8(6)	186.0(6) 185.8(5)	–

[a] C1–S1 (top) and C1–S2 (bottom) distances; [b] S1–C(F_3) (top) and S2–C(F_3) (bottom) distances; [c] C3–P1 distance.

To obtain an accurate understanding of the electronic states in the carbabetaines, we optimized the experimental geometries of *anti* conformer **5a** and *syn* conformer **5i** by using hybrid DFT calculations at the M06-2x level of theory with the 6-311++G(d,p) basis set (Table 1).[19] The potential-energy minima were established in combination with frequency analysis. Natural bond orbital (NBO) theory[20] and Bader's quantum theory of atoms in molecules (QTAIM)[21] were applied to the optimized geometries. For compound **5a**, the natural population analysis (NPA) charge of the C1 atom was calculated to be −0.93 *e* (for atom numbering, see Figures 2 and 3). According to the QTAIM analysis, the charge was −0.46 *e*. On the other hand, the charge on the P1 atom was +1.60 *e* and +2.46 *e* from the NBO and QTAIM analysis, respectively. Similar magnitudes of the atomic charges were obtained for compound **5i**. These values were consistent with the anionic and cationic character of the respective moieties. In both compounds **5a** and **5i**, NBO calculations revealed a p orbital (LP_{C1}) at the C1 atom with suitable electron occupancy (**5a**: 1.69 *e*; **5i**: 1.68 *e*). In this case, the second-order perturbation of the LP_{C1} orbital to adjacent $\sigma^*_{S-C(F_3)}$ orbitals was notably strong (stabilization energy >20 kcal mol^{-1}). This result supported the importance of negative hyperconjugation. In addition, the natural localized molecular orbital (NLMO)/NPA bond order of the C1–S bond was larger than those of the S–C(F_3) bonds (C1–S: 0.92–0.95; S–C(F_3): 0.72–0.75). The same trend was observed in the QTAIM analysis; for example, a larger electron density (ρ_{BCP}) and larger negative Laplacian ($\nabla^2\rho_{BCP}$) at the bond critical point (BCP) were observed, as well as a larger delocalization index (see the Supporting Information). Note that the delocalization of the LP_{C1} bond to the sulfonic oxygen atoms was a

subordinate stabilizing effect. The bond order of the S–O bond in organic sulfones was typically less than 1.5 (not 2), as mentioned in both theoretical and experimental studies.[22] In other words, the contribution of a widely accepted "S=O" resonance structure was significantly limited. The LP_{C1}/σ^*_{C2-P1} interactions in compounds **5a** and **5i** were 12.9 and 17.6 kcal mol^{-1}, respectively. In light of the NBO analysis of the pyridinium zwitterion, this interaction was about 1.5-times weaker than the $LP_{C(-)}/\sigma^*_{C\text{-}N(+)}$ interaction (see the Supporting Information).

The QTAIM analysis is a powerful tool for analyzing relatively weak interactions. For both compounds **5a** and **5i**, bond paths from the anionic C1 atom to the P1 atom, as well as to the sulfonic oxygen atoms, were not found (Figure 3). Beyond the bond paths for covalent bonds, a bond path from the C1 atom to the C4 atom in the phenyl group was only observed in compound **5a**. Based on its bond parameters (ρ_{BCP}: 0.0090 *e* bohr^{-3}; $\nabla^2\rho_{BCP}$: 0.0260 *e* bohr^{-5}; total electron energy density, K_{BCP}: −0.00008), we observed slight charge-transfer (CT) character.[23] In the NBO analysis, a weak LP_{C1}/π^*_{C4-C5} interaction (1.3 kcal mol^{-1}) was also observed. In addition, some bond paths from the sulfonic oxygen or fluorine atoms to the hydrogen or carbon atoms on the aryl groups were observed in both cases. In contrast, QTAIM analysis of phosphonium enolate **1a**[7] as a reference compound exhibited a pronounced bond path between the O1 and P1 atoms, which could be clearly classified as a CT interaction based on its bond parameters (ρ_{BCP}: 0.0519 *e* bohr^{-3}; $\nabla^2\rho_{BCP}$: 0.0724 *e* bohr^{-5}; K_{BCP}: 0.0108). In the optimized structure of compound **1**, the P1 atom adopted a pseudotrigonal-bipyramidal structure. As shown in Figure 4, the $\nabla^2\rho_{BCP}$ contours and the overlap of the LP_{O1} and σ^*_{P1-C4} orbitals, with a stabilization energy of 20.1 kcal mol^{-1}, allow the visualization of this interaction.

To understand such a sharp contrast, steric congestion around the phosphorus atom should also be considered. Therefore, we also analyzed diphenyl(phenylethynyl) and trimethyl derivatives **5l** and **5a-Me**, respectively (see the Supporting Information). In both cases, there were no bond paths to the phosphorus atom, not only from the anionic carbon atom, but also from the oxygen and fluorine atoms. The lack of direct bond paths between the anionic carbon atoms and the cationic phosphorus atoms did not preclude the existence of any attractive interactions between the anionic and cationic parts.[24] This analyses revealed a number of weak noncovalent interactions between the R_3P^+ and the $[Tf_2C]^-$ groups, sometimes termed "anion···π" and "anion···H–C" interactions,[25] which served as a stabilizing factor of the structures. In the $[Tf_2C]^-$ structure, negative hyperconjugation, as well as steric congestion around the anionic carbon atom, played a key role in suppressing direct CT interactions with the cationic phosphorus atom.

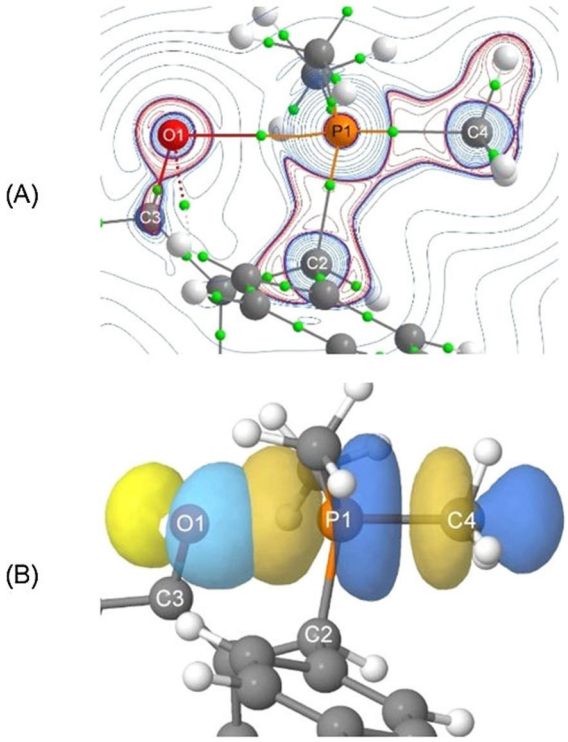


Figure 4. QTAIM and NBO projections of the O1···P1–C4 interactions in compound **1a**: A) positive (red) and negative (blue) Laplacians; B) overlap between the $LP(2)_{O1}$ and σ^*_{P1-C4} orbitals.

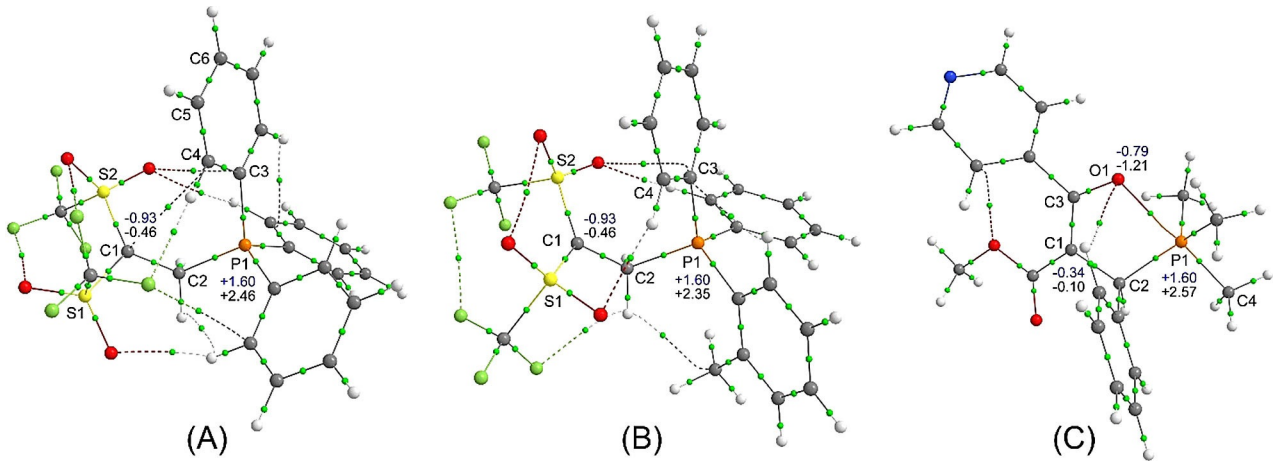


Figure 3. Bond critical points (green spheres) from the QTAIM analysis and key atomic charges (top: NPA charge; bottom: QTAIM charge) for A) **5a**; B) **5i**; and C) **1a**.

3. Conclusion

We have successfully synthesized 1,3- and 1,4-carbabetaines **5** and **6** by using in-situ-generated $Tf_2C{=}CH_2$ (**4**). X-ray crystallographic analyses of the products clearly showed that any attractive interactions between the cationic and anionic moieties were negligibly weak. Compared with reference compound **1a**, which exhibited a clear '$O^-{\cdots}P^{+\prime}$ charge-transfer interaction, carbabetaines **5** and **6** did not exhibit any direct interatomic interactions between the anionic and cationic moieties by using NBO and QTAIM analyses. However, some weak interactions collectively served to stabilize their molecular structure. Based on these results, these compounds represent the first examples of well-defined carbabetaines. We have also provided greater insight into the stability of the $[Tf_2CR]^-$ ion. In particular, the importance of negative hyperconjugation in the stability of the $[Tf_2CR]^-$ anion was quantitatively established.

Experimental Section

Synthesis of 1,1-Bis((trifluoromethyl)sulfonyl)-2-(triphenylphosphonio)ethan-1-ide (5a)

2-Fluoropyridinium salt **3** (38.0 mg, 97.6 μmol) was added to a solution of triphenylphosphine (26.5 mg, 101 μmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2 (3×2 mL) to give the product in 99% yield (53.7 mg, 96.9 μmol). The structure of the product was confirmed by single-crystal X-ray crystallographic analysis.

Colorless crystals (from $CHCl_3$); m.p. 238–240 °C; ^{1}H NMR (500 MHz, CD_3CN): δ = 4.31 (br s, 2H), 7.63–7.71 (m, 12H), 7.80–7.87 ppm (m, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 30.0 (d, J(C,P) = 51.4 Hz), 57.8, 119.7 (d, J(C,P) = 84.2 Hz), 121.99 (q, J(C,F) = 327 Hz), 122.03 (q, J(C,F) = 328 Hz), 130.7 (d, J(C,P) = 12.5 Hz), 135.4 (d, J(C,P) = 9.3 Hz), 135.6 ppm (d, J(C,P) = 2.5 Hz); ^{19}F NMR (376 Hz, CD_3CN): δ = −16.3 ppm (s, 6F); ^{31}P{^{1}H} NMR (162 Hz, CD_3CN): δ = 23.2 ppm; IR (ATR): $\tilde{\nu}$ = 2971, 1439, 1347, 1162, 1108, 994, 723, 688, 606, 488 cm^{-1}; MS (ESI-TOF): m/z: 555 $[M+H]^+$; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{17}F_6O_4PS_2$: 555.0288 $[M+H]^+$; found: 555.0286.

Synthesis of 2-(Diphenyl(o-tolyl)phosphonio)-1,1-bis((trifluoromethyl)sulfonyl)-ethan-1-ide (5i)

2-Fluoropyridinium salt **3** (40.0 mg, 103 μmol) was added to a solution of diphenyl(*o*-tolyl)phosphine (28.4 mg, 103 μmol) in MeCN (1.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2 (3×2 mL) to give the product in 93% yield (54.4 mg, 95.7 μmol). The structure of the product was confirmed by single-crystal X-ray crystallographic analysis.

Colorless crystals (from CH_2Cl_2); m.p. 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 4.35 (br s, 2H), 7.37–7.45 (m, 2H), 7.46–7.54 (m, 1H), 7.63–7.73 (m, 9H), 7.78–7.85 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.1 (d, J(C,P) = 3.8 Hz), 30.6 (d, J(C,P) = 48.1 Hz), 57.2, 117.8 (d, J(C,P) = 79.5 Hz), 118.1 (d, J(C,P) = 80.0 Hz), 120.95 (q, J(C,F) = 328 Hz), 120.99 (q, J(C,F) = 328 Hz), 127.2 (d, J(C,P) = 12.3 Hz), 130.0 (d, J(C,P) = 12.4 Hz), 133.6 (d, J(C,P) = 11.1 Hz), 134.5 (d, J(C,P) = 8.9 Hz), 134.8 (d, J(C,P) = 2.5 Hz), 134.9 (d, J(C,P) = 2.5 Hz), 135.4 (d, J(C,P) = 10.2 Hz), 143.0 ppm (d, J(C,P) = 9.0 Hz); ^{19}F NMR (376 Hz, $CDCl_3$): δ = −15.6 (s, 6F); ^{31}P{^{1}H} NMR (162 Hz, $CDCl_3$): δ = 22.2 ppm; IR (ATR): $\tilde{\nu}$ = 1438, 1345, 1173, 1155, 1097, 719, 598, 578, 475 cm^{-1}; MS (ESI-TOF): m/z: 596 $[M+H]^+$; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}F_6O_4PS_2$: 569.0445 $[M+H]^+$; found: 569.0443; elemental analysis calcd (%) for $C_{23}H_{19}F_6O_4PS_2$: C 48.59, H 3.37; found: C 48.36, H 3.50.

Synthesis of 2-(Tributylphosphonio)-1,1-bis((trifluoromethyl)-sulfonyl)ethan-1-ide (5j)

2-Fluoropyridinium salt **3** (78.7 mg, 202 μmol) was added to a solution of tributylphosphine (50 μL, 203 μmol) in MeCN (2.0 mL) at RT. The mixture was stirred for 15 min and then concentrated under reduced pressure. The resulting solid was washed with *n*-hexane (3×2 mL) to give the product in 94% yield (93.8 mg, 190 μmol).

Colorless crystals (from CH_2Cl_2); m.p. 76.0–77.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, J = 6.9 Hz, 9H), 1.45–1.59 (m, 12H), 2.09–2.18 (m, 6H), 3.20 ppm (d, J(C,P) = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2, 18.9 (d, J(C,P) = 46.2 Hz), 21.4 (d, J(C,P) = 51.5 Hz), 23.2 (d, J(C,P) = 4.6 Hz), 23.8 (d, J(C,P) = 14.8 Hz), 56.1, 121.2 (q, J(C,F) = 328 Hz), 121.3 ppm (q, J(C,F) = 328 Hz); ^{19}F NMR (376 Hz, $CDCl_3$): δ = −15.2 ppm (s, 6F); ^{31}P{^{1}H} NMR (162 Hz, $CDCl_3$): δ = 33.1 ppm; IR (ATR): $\tilde{\nu}$ = 2966, 2938, 1344, 1158, 1099, 999, 608, 576, 505 cm^{-1}; MS (ESI-TOF): m/z: 517 $[M+Na]^+$; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{29}F_6NaO_4PS_2$: 517.1047 $[M+Na]^+$; found: 517.1038; elemental analysis calcd (%) for $C_{16}H_{29}F_6O_4PS_2$: C 38.86, H 5.91; found: C 38.96, H 5.78.

Synthesis of 1,1-Bis((trifluoromethyl)sulfonyl)-3-(triphenylphosphonio)propan-1-ide (6a)

*n*BuLi (1.55 M in *n*-hexane, 0.25 mL, 0.39 mmol) was added to a solution of methyltriphenylphosphonium bromide (146 mg, 0.410 mmol) in THF (2.0 mL) at 0 °C. The mixture was stirred for 30 min and then 2-fluoropyridinium salt **3** (76.3 mg, 0.196 mmol) was added. Stirring was continued at RT for a further 2 h. Then, a saturated aqueous solution of NH_4Cl (20 mL) was added to quench the reaction. After extraction with EtOAc (3×20 mL), the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography on neutral silica gel ($CHCl_3$/MeOH, 70:1) to give an impure material that mainly consisted of the desired product. This material was washed with *n*-hexane/Et_2O (1:1, 3×2 mL) to give the pure product in 62% yield (69.6 mg, 0.122 mmol). The structure of the product was confirmed by single-crystal X-ray crystallographic analysis.

Colorless crystals (from EtOAc); m.p. > 250 °C (dec.); ^{1}H NMR (500 MHz, CD_3CN): δ = 2.78 (br s, 2H), 3.41 (br s, 2H), 7.55–7.66 (m, 6H), 7.66–7.75 (m, 6H), 7.80–7.87 ppm (m, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 23.2, 25.6 (d, J(C,P) = 43.0 Hz), 62.9, 118.0 (d, J(C,P) = 85.5 Hz), 121.2 (q, J(C,F) = 328 Hz), 130.7 (d, J(C,P) = 12.6 Hz), 133.2 (d, J(C,P) = 10.0 Hz), 135.4 ppm (d, J(C,P) = 3.1 Hz); ^{19}F NMR (376 Hz, CD_3CN): δ = −16.7 ppm (s, 6F); ^{31}P{^{1}H} NMR (162 Hz, CD_3CN): δ = 21.3 ppm; IR (ATR): $\tilde{\nu}$ = 2924, 1346, 1190, 1160, 1112, 1206, 689, 578, 506 cm^{-1}; MS (ESI-TOF): m/z: 591 $[M+Na]^+$; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{19}F_6NaO_4PS_2$: 591.0264 $[M+Na]^+$; found: 591.0267.

Computational Methods

Structure-optimization calculations and frequency analysis were performed by using the Gaussian 09 program package, revision D.01.[26] NBO and QTAIM analyses were performed by using the NBO 6.0 and AIMAll programs, respectively.[27,28] All of the calculations were performed at the M06-2x/6-311++G(d,p) level of

theory. For the NBO calculations, single-point calculations with DFT-optimized geometries at the HF/def2-TZVPP[29] level of theory were also applied. The geometries were visualized by using the CYLview program.[30] NBOs were visualized by using Jmol, with the Jmol-NBO Visualization Helper.[31]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbabetaines · carbanions · phosphorus · structure elucidation · X-ray diffraction

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Transition metal-free controlled synthesis of bis[(trifluoromethyl)sulfonyl]ethyl-decorated heterocycles†‡

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Several heterocycles reacted with shelf-stable 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl] ethan-1-ide, a latent $Tf_2C{=}CH_2$ source, to give rise in a mild and controllable way to adducts *via* direct C–H bis[(trifluoromethyl)sulfonyl]ethylation reactions. This metal- and irradiation-free protocol is convenient. Besides, the volatile side-product 2-fluoropyridine can be smoothly eliminated under vacuum, which facilitates purification. The substrate scope survey discloses that exquisite chemo- and regioselectivities are achieved in a variety of heterocyclic systems. Of particular interest are the late-stage structural modification of known pharmaceuticals, such as the marketed drugs Phenazone (Antipyrine) and Edaravone, and the development of a water soluble fluorescent dye.

Introduction

Heterocyclic scaffolds have fascinated chemists due to their widespread occurrence in bioactive compounds, functionalized dyes, and advanced materials. To improve the molecular functions of the heterocyclic compounds through regulating the physicochemical properties, incorporation of an additional functionality into the heterocyclic scaffolds is a common approach. In particular, fluorine-containing functionalities attract much attention because organic molecules having fluorinated functionalities display notable differences from their non-fluorinated counterparts in both their physicochemical and pharmacological properties.[1] A pivotal issue for efficient organic synthesis is the transformation of readily available precursors into target molecules in the fewest possible steps with a minimization of labour and waste. Demands for the efficient generation of diverse heterocyclic compounds bearing fluorinated substituents continue to stimulate the development of versatile synthetic strategies through late-stage structural modification. For example, fluoroalkyl heterocycles can be ideally prepared *via* direct C–H fluoroalkylation. However, the straightforward and selective fluoroalkylation of heterocycles is still a difficult task.[2,3] Besides, it should be taken into account that transition metal-catalyzed protocols raise safety concerns in medicinal and engineering applications due to the presence of metal impurities in the organic products.

In recent years, much attention has been paid to heterocycles bearing the trifluoromethylsulfonyl (trifyl) group (Tf = SO_2CF_3). The triflyl group is one of the strongest electron-withdrawing substituents and it can endow the molecules with mild lipophilicity. Consequently, different strategies have been developed to prepare trifluoromethyl sulfones.[4] The electron-withdrawing effect of the triflyl group also makes compounds bearing the *gem*-bis(triflyl)methyl group (Tf_2CH) strongly acidic. The acidity of such C–H acids is comparable to that of sulfuric acid;[5] therefore the Tf_2CH group has been already used as a key functionality in the development of highly effective acid catalysts.[4c,e,6] However, installing the Tf_2CH group into the heterocyclic scaffolds has not been reported. One of the serious drawbacks is relatively strong basicity of nitrogen-containing heterocycles. As an effective methodology for Tf_2CH-functionalization, Yanai *et al.* reported the bis(triflyl) ethylation reaction of neutral nucleophiles such as phenols

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† Dedicated to Prof. M. Pilar Ruiz on the occasion of her retirement.

‡ Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, crystallographic details, and copies of NMR spectra for all new compounds. CCDC 1832225–1832230, 1833410 and 1843015. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8qo00955d

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Metal-free [3+2] cycloaddition of azides with $Tf_2C{=}CH_2$ for the regioselective preparation of elusive 4-(trifluoromethylsulfonyl)-1,2,3-triazoles†

Benito Alcaide,*[a] Pedro Almendros*[b] and Carlos Lázaro-Milla[a]

1,2-Dipole $Tf_2C{=}CH_2$ is generated *in situ* and immediately reacts at room temperature with an azide to afford previously unknown 4-trifluoromethanesulfonyl 1,2,3-triazoles through a stepwise [3+2] cycloaddition reaction. Noteworthily, this mild and powerful uncatalyzed protocol is highly regio- and chemoselective.

Substituted 1,2,3-triazoles are among the most important heterocyclic systems. They have found widespread applications in drug discovery, chemical biology, supramolecular chemistry and materials science.[1–9] 1,2,3-Triazoles are also useful precursors for the construction of more complex structures.[10–16] The classical route for the construction of the 1,2,3-triazole ring is achieved *via* the thermal Huisgen 1,3-dipolar cycloaddition of alkynes to azides.[17,18] This traditional protocol presents serious drawbacks because of the requirement for elevated temperatures and poor regioselectivity, resulting in a mixture of 1,4- and 1,5-regioisomers. Metal-catalyzed strategies have been merged recently for the regioselective formation of triazoles through alkyne–azide 1,3-dipolar cycloaddition (AAC). Of particular interest are the copper-,[19–22] ruthenium-,[23,24] silver-,[25] and gold-catalyzed[26] AACs. However, the widespread use of these metal-based triazole synthesis protocols for biological applications is precluded due to the cytotoxicity and eco-adverse effects of the heavy metals. Although several non-metal protocols have been described,[27–35] nowadays, there is an increasing interest in efficient metal-free strategies for the synthesis of the 1,2,3-triazole nucleus.

Fluoroorganic molecules exhibit peculiar biological activities because of their improved lipophilicity and metabolic stability.[36–39] The trifluoromethanesulfonyl moiety is particularly relevant due to its effectiveness for the modification of the chemical properties of organic compounds without changing molecular complexities.[40] *N*-Triflyl triazoles, whose reactivity can be further exploited,[41] are available taking advantage of the sulfonylation of *NH*-triazoles in the presence of triflic anhydride. Surprisingly, the preparation of the *C*-trifluoromethanesulfonylated triazole moiety counterpart has not been reported. The synthesis of carbon-substituted triflyl triazoles may be precluded by their unavailability through the widely used AAC.

We envisioned that the highly polarized 1,1-bis(trifluoromethylsulfonyl)ethene **1** may be an effective reagent for the synthesis of *C*-triflyl triazoles through the reaction with azides. $Tf_2C{=}CH_2$ **1** reacts with alkynes and 1,3-dienes to give the corresponding *gem*-bis(triflyl)-cyclobutenes and *gem*-bis(triflyl)-cyclohexenes.[42,43] Additionally, 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** has been identified as a stable precursor of **1** with the transfer of the Tf_2CH group to phenols.[44] In this context, we now wanted to explore whether the reaction of pyridinium salt **2** with organic azides would open access to previously unknown *C*-triflyl 1,2,3-triazoles *via* a mild metal-free protocol.

The evaluation of the initial hypothesis was carried out using the readily available benzyl azide **3a**. In a first experiment with benzyl azide, we wanted to investigate whether or not the competing activation of the azide substrate **3a** was observed during its treatment with the reactive but sterically demanding species **1**. This was crucial as such a reactivity lacking the 1,3-dipolar cycloaddition pathway would provide undesired products. A strong solvent dependence was observed. Optimization of the solvent was limited by the insolubility of zwitterion **2** in solvents such as dichloromethane, benzene and tetrahydrofuran, resulting in heterogeneous reaction conditions. Among the examined solvents, acetonitrile, dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were chosen to further optimize the reaction conditions because of the high solubility of precursor **2** in these media. While DMSO and DMF were found to be unacceptable choices because of the overall low yields and the formation of byproducts, acetonitrile was the optimal solvent. Outstandingly, the reaction of benzyl

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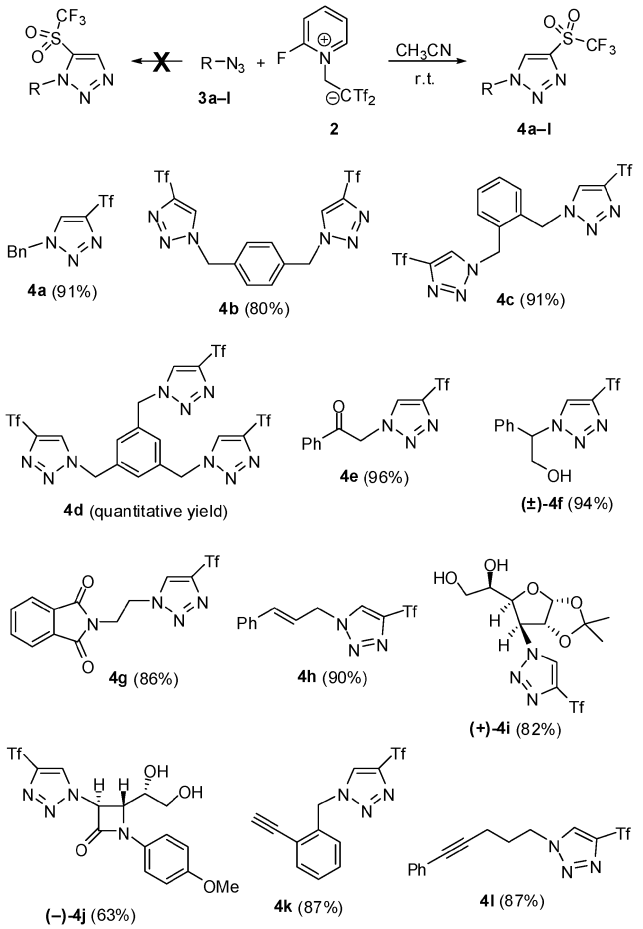
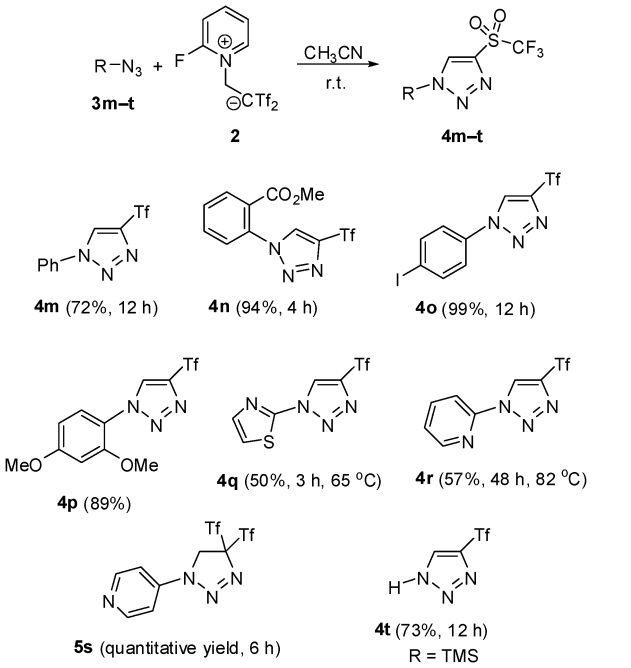


Scheme 1 Uncatalyzed synthesis of 1-alkyl-4-triflyl triazoles **4a–l** at room temperature from substituted alkyl azides **3a–l** and zwitterion **2**.

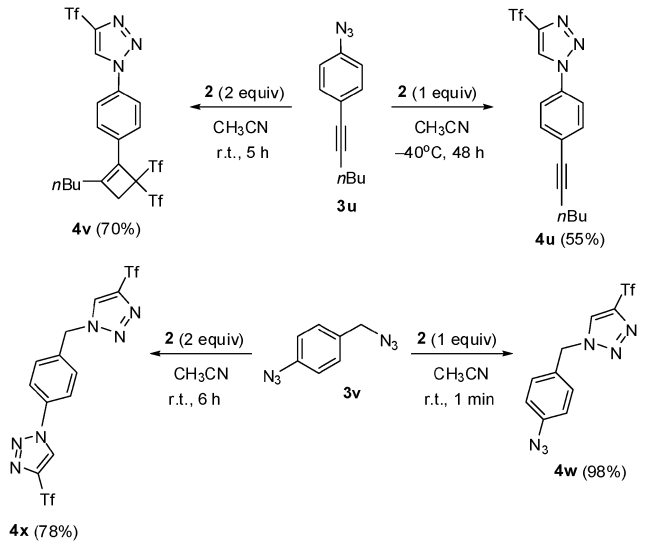


Scheme 2 Uncatalyzed synthesis of 1-aryl-4-triflyl triazoles **4m–r** at room temperature from substituted aryl azides **3m–r** and zwitterion **2**.

azide **3a** with 1 equiv. of the zwitterionic reagent **2** in acetonitrile at room temperature led to an almost quantitative yield of the desired *C*-triflyl triazole **4a** (Scheme 1). Notably, the cyclization reaction of **3a** in the presence of 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **2** could be used in a large-scale reaction to afford **4a** in a similar yield. Spurred by the excellent results observed with benzyl azide, we examined the reactivity of a variety of azides under the above conditions. The results are presented in Scheme 1. Aliphatic azides **3a–l**, including allylic and phenacyl azides, instantaneously reacted to afford the corresponding *C*-triflyl triazoles **4a–l** in excellent yields.[45] The use of diazides **3b** and **3c** and triazide **3d** as substrates allowed the synthesis of bis(triazoles) **4b** and **4c** and tris(triazole) **4d**, respectively. The mildness of the method did allow the use of enantiopure starting azides **3i** and **3j**. Reasonable yields of sugar- and β-lactam-linked triazoles **4i** and **4j** were observed without erosion of the stereochemical integrities (Scheme 1).[46] As is evident from the results shown in Scheme 1, total chemoselectivity was achieved because the reaction of the alkyne moiety was not observed in alkynyl azides **3k** and **3l**. The above results are of particular importance considering the fact that either intermolecular or intramolecular reactions of azides with alkynes usually afford triazoles.

This metal-free method was applicable not only to aliphatic azides but also to aromatic ones; and the corresponding *C*-trifluoromethanesulfonylated triazoles **4m–r** were furnished in high yields under mild conditions (Scheme 2). While the reactions of alkyl azides **3a–l** were instantaneous, the reactions of their aromatic counterparts **3m–s** took several hours at room temperature. Interestingly, the formation of triazole **4p** from the electron-rich arene-containing azide **3p** was immediate. Heteroaromatic azides **3q** and **3r** also provided the desired 4-triflyl triazoles **4q** and **4r**, but after gentle heating (Scheme 2). Azide **3s** exclusively afforded 4-[4,4-bis(trifluoromethylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl]pyridine **5s**, but the aromatic adduct **4s** could not be obtained (Scheme 2). Upon the evaluation of the substrate scope for this transformation, we observed that trimethylsilyl (TMS) azide was also a suitable starting material. In the event, the formation of 4-triflyl triazole **4t** lacking the TMS group was observed (Scheme 2).

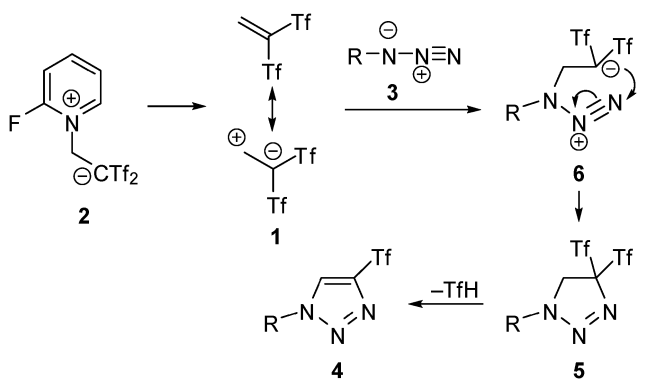
Under the optimized reaction conditions, the cyclobutenyl triazole **4v** was obtained in a reasonable yield from alkynyl azide **3u**. A temperature effect was observed by performing the reaction at low temperature (−40 °C), and the alkynyl triazole **4u** was exclusively formed (Scheme 3). The selective monofunctionalization of diazide **3v** bearing both aromatic and aliphatic azide moieties into 4-triflyl triazole **4w**, as well as the two-fold reaction to form bis(triazole) **4x** were also successfully developed (Scheme 3). Interestingly, the mildness of the protocol allows the chemocontrol and the discrimination in reactivity of the alkyl azide functionality (which underwent faster reaction rate) *versus* the corresponding reference aryl azide in **3v**. Noteworthily, the above-disclosed chemoselectivity issues that are otherwise difficult to address using the AAC, have been easily resolved using our method.



Scheme 3 Controlled reactivity of alkynyl azide **3u** and diazide **3v**.

A conceivable mechanism for the formation of 4-trifluoromethanesulfonyl 1,2,3-triazoles **4** from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **2** and organic azides **3** is shown in Scheme 4. It may initially involve the formation of 1,1-bis(trifluoromethylsulfonyl)ethene **1** from zwitterion **2**. Next, the stepwise [3+2] cycloaddition reaction between azides **3** and the *in situ* generated 1,2-dipole **1**,[47] initially leading to the zwitterionic species **6** should take place. This addition product, zwitterion **6**, initiates a ring-closure reaction and produces the intermediate 1-substituted-4,4-bis(trifluoromethylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazoles **5**.[48] The formation of species **5** could trigger a rapid trifluoro(hydrosulfonyl)methane (TFH) elimination, thus leading to the final 4-triflyl 1,2,3-triazoles **4**. Possibly, the driving force of this process may be related to the gain in aromaticity associated with the triazole formation.

In conclusion, 2-(2-fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide has been used as a precursor of the highly polarized 1,1-bis(trifluoromethylsulfonyl)ethene species $Tf_2C{=}CH_2$ in a metal-free stepwise [3+2] cycloaddition reaction of azides. This straightforward approach gives access, for the first time, to the previously elusive 4-trifluoromethanesulfonyl 1,2,3-triazoles from simple starting materials. Besides, the method is highly chemoselective and the reactions have been carried out at room temperature without the requirement of metals, bases or additives.



Scheme 4 Rationalization for the synthesis of 4-triflyl triazoles **4** from organic azides **3** and zwitterion **2**.

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45 The regiochemistry of products **4** was unambiguously determined by the NOE analysis of **4h**.
46 Dihydroxy-triazoles **4i** and **4j** were in conformational equilibrium and the conformers were observed using NMR spectroscopy. Both conformers were equilibrated after several hours in solution and converted into just one isomer.
47 Especies **1** is better described as a resonance hybrid between both dipolar and uncharged species.
48 Although the isolation of 4,5-dihydro-1*H*-1,2,3-triazole **5s** through the reaction of **3s** outlined in Scheme 2 was fortuitous, the result argues in favor of the mechanism shown in Scheme 4 because an observable intermediate of type **5** was formed.

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Photoinduced Gold-Catalyzed Domino C(sp) Arylation/Oxyarylation of TMS-Terminated Alkynols with Arenediazonium Salts

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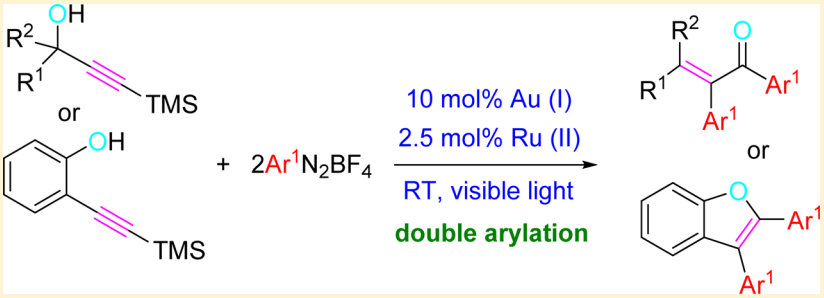
Supporting Information



ABSTRACT: A selective and convenient synthesis of tri- and tetrasubstituted α,β-unsaturated ketones, as well as 2,3-diarylbenzofurans has been developed with the aid of light and taking advantage of a cooperative gold/photoredox-catalyzed 2-fold arylation reaction of TMS-terminated alkynols. The reaction of 3-(trimethylsilyl)prop-2-yn-1-ols was competent to generate diarylated α,β-unsaturated ketones; whereas the photoredox sequence involving 2-[(trimethylsilyl)ethynyl]phenol exclusively afforded 2,3-diarylbenzofurans. The reaction of terminal alkynes proceeded in poor yields while the use of bulkier silyl groups, such as TIPS, resulted unproductive. Apparently, the C(sp) arylation reaction is the first event on the domino bis-arylative sequence. These results could be explained through the intermediation of arylgold(III) species and several single electron transfer processes.

INTRODUCTION

The ready availability of diazonium salts makes these compounds as widely applicable building blocks in organic chemistry.[1] Arenediazonium salts react without the assistance of any ligand or base and are one of the most sustainable and convenient alternatives to aryl halides. Aiming to reduce waste, organic chemists have been trying to develop visible-light photoredox catalysis as a tool in synthetic chemistry.[2] Organometallic complexes (ruthenium- and iridium-based) and metal-free organic dyes (eosin Y, rose bengal, rhodamine B, fluorescein) have been successfully incorporated in the recently developed gold-catalyzed photoredox chemistry.[3] Early work in gold catalysis demonstrated that even dinuclear complexes of gold can serve as photoredox catalysts,[4] a principle which has been taken up very successfully in gold-only photoredox chemistry.[5] This new approach represents an attractive, eco-friendly alternative to the addition of strong oxidants in stoichiometric excess for accessing to Au(I)/Au(III) catalytic cycles.[6]

The α,β-unsaturated ketone as well as the benzofuran motifs constitute an important class of compounds because they are found in numerous biologically active natural products and serve as starting materials to prepare a variety of organic compounds. We and others have recently established that, with the aid of a photoredox catalyst, an array of α,β-unsaturated ketones can be obtained from alkynols through a gold-catalyzed Meyer−Schuster/arylation reaction sequence promoted by visible light (Scheme 1a).[7] Domino reactions are practical one-step methods for accessing organic compounds which require less energy and labor.[8] Herein, we take advantage of a photocatalyzed system to develop a selective domino gold-catalyzed 2-fold arylation reaction of TMS-terminated alkynols to produce different diarylated α,β-unsaturated ketones and 2,3-diarylbenzofurans (Scheme 1b).

RESULTS AND DISCUSSION

Several challenges had to be considered in the design of the double arylation sequence, mainly to address the chemoselectivity issue. Depending on the reactivity of the terminal alkynol, two different isomeric products can be initially produced, the aryl-substituted alkynol through Hiyama−Sonogashira-type coupling, and the monoarylated α,β-unsaturated ketone through Meyer−Schuster-type reaction (or the monoarylated benzofuran through intramolecular alkoxylation). For the success of the domino sequence, the reaction should give access first to the C(sp) arylation event.[9] We set out to

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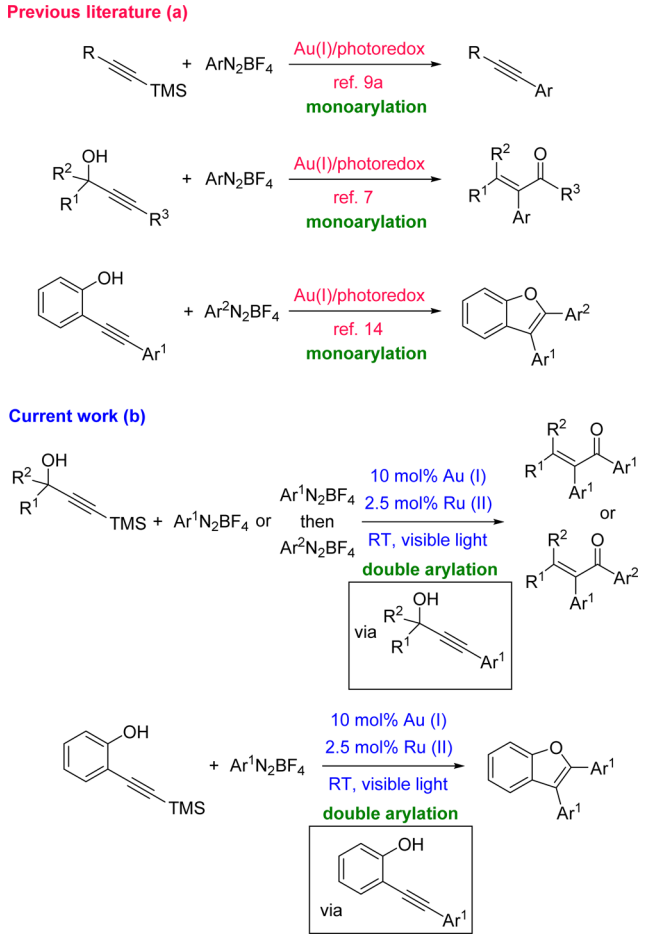
Scheme 1. Generic Scheme Delineating the Photopromoted Mono- and Bis-Arylative Reactions of Alkynols



probe the validity of our design by using terminal alkynol **1a** as starting material and six equivalents of 4-bromophenyldiazonium salt **2b** under the visible light-driven optimal conditions identified earlier in our laboratory, namely, in the presence of both Gagosz's catalyst $[(Ph_3P)AuNTf_2]$ and the photoactive ruthenium complex $[Ru(bpy)_3](PF_6)_2$ (bpy =2,2′-bipyridine) (Scheme 2). In this case, the desired diarylated product **3ab** was obtained in only 35% yield (Table 1, entry 1). To improve the yield of the required diaryl adduct, other alkynic substrates were screened. To our delight, with TMS-derivative **4a** as precursor, the double arylation reaction was more efficient, giving rise to **3ab** in a great 82% yield without apparent impact on the reaction rate (Table 1, entry 2). Besides, the reaction proceeded with total stereochemical control, giving rise exclusively to the *E*-isomer. The catalyst loading of the gold salt could be reduced to 5% without considerable erosion in the

Table 1. Modified Conditions for the Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Alkynols with Arenediazonium Salts[a]

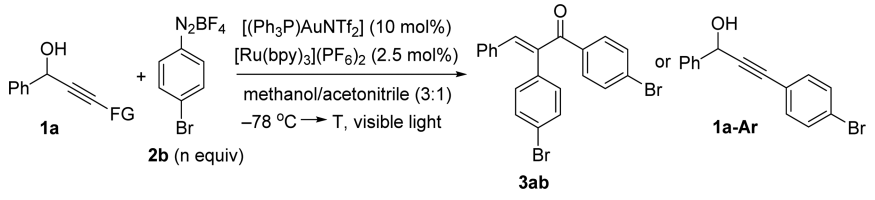
entry	FG	*n*	*T*	*t* (h)	yield[b]
1	H	6	RT	4	**3ab** (35%)
2	TMS	6	RT	4	**3ab** (82%)
3	TMS	6	RT	4	**3ab** (40%)[b]
4	TMS	12	RT	4	**3ab** (80%)
5	TMS	1	−20 °C	0.5	**1a-Ar** (65%)
6	TIPS	6	RT	4	**3ab** (<5%)

[a]Reaction was carried out using PPh_3AuCl as the gold catalyst. [b]Yield of pure, isolated product with correct analytical and spectral data.

reaction yield. Further reduction of the gold catalyst loading to 2% resulted in a reaction mixture which includes appreciable amounts of unreacted starting material. The reaction yield could not be improved when PPh_3AuCl was applied as catalyst (Table 1, entry 3). The use of twice (12 equiv) as much arenediazonium salt **2b** neither did increase the yield of the target product (Table 1, entry 4), as the reaction was then complicated by chromatographic separation. It is shown that arylative Meyer−Schuster rearrangement is not in competition with the C(sp) arylation (Hiyama−Sonogashira-type coupling), because *α,β*-unsaturated ketone formation did not occur with the addition of just one equivalent of arenediazonium salt (Table 1, entry 5). On the other hand, sterically more demanding TIPS greatly retarded the reaction, resulting in a low conversion with the formation of only trace amounts of **3ab** (Table 1, entry 6).

Control experiments proved that the gold salt, the photocatalyst, and light are all together required for the 2-fold arylation sequence to proceed. With the optimized reaction conditions in hand, we examined the scope of the reaction of TMS-alkynol **4a** with differently substituted arenediazonium salts **2**. Several functional groups were well-tolerated under the reaction conditions. The products (**3aa**−**3al**) were obtained in moderate to good yields, and the results are summarized in Scheme 3. It is observed that the substituent at the diazonium salts **2a**−**l** did exert a significant influence. It can be noted that the reaction is much efficient with neutral and somewhat electron poor arenediazonium salts. Strongly electron-withdrawing groups did afford the corresponding NO_2- and CF_3-diarylderivatives **3af** and **3ag** in low yields, while electron-donating groups, such as MeO and Me (diazonium salts **2i** and **2j**) did not afford the corresponding diarylated products **3ai** and **3aj**. Additionally, the steric effect was obvious because an *ortho* bromine substituent led to a low yield of the monoarylated *α,β*-unsaturated ketone **5l**. Probably, the 2-bromoaryl substituent may block the second arylation step. Noteworthy, the carbon−halide bonds in **3aa**−**3ae** and **3ak**, which could serve as reactive handle for further manipulation,

Scheme 2. Selective Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Alkynols with Arenediazonium Salts



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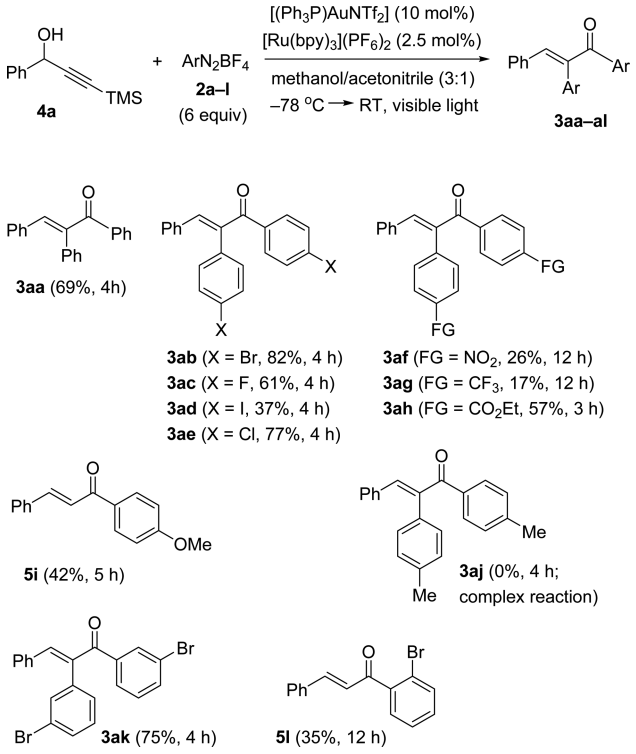
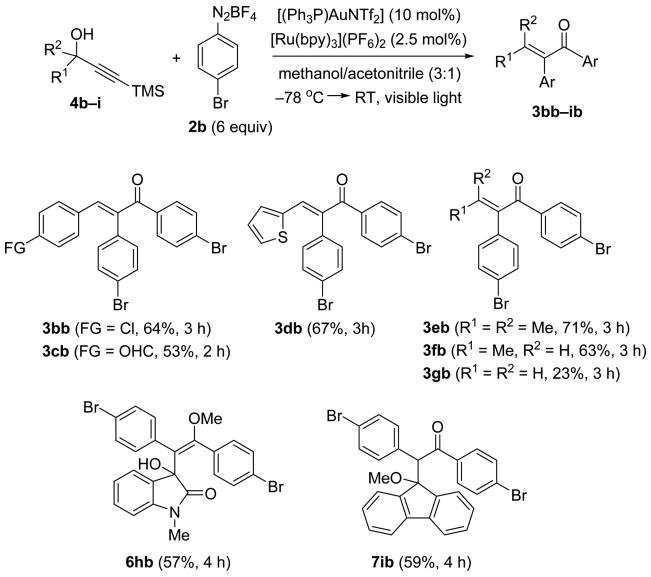
Scheme 3. Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Alkynol 4a with Arenediazonium Salts



were not affected under the dual gold-photoredox conditions. Taking into account the reactivity of C–X bonds under conventional cross-coupling conditions, our protocol is a promising alternative to these classical reactions.

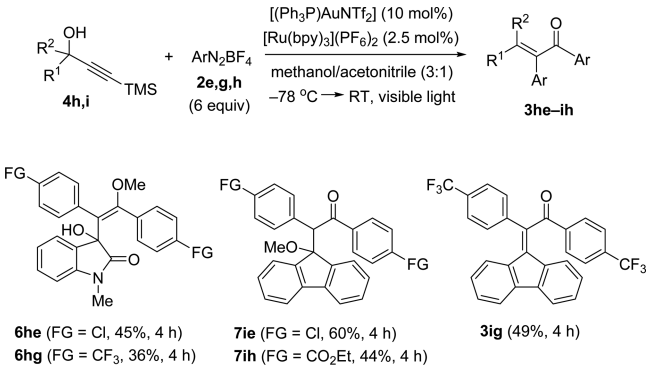
Under the optimized conditions, the scope of the arylation/oxyarylation sequence was investigated through the reaction of arenediazonium salt **2b** with various trimethylsilyl alkynols **4b–i**. Starting from functionalized TMS-alkynols bearing a variety of substituents, such as the thiophene ring, the domino reaction also smoothly proceeded and gave rise to the products **3bb–3ib** in reasonable yields (Scheme 4). Noticeably, the diarylation sequence occurred with total stereoselectivity for providing single *E*-isomers. The reactions of the alkyl- or dialkyl-substituted TMS-alkynols **4e** and **4f** also efficiently took place, and the corresponding diarylated α,β-unsaturated ketones **3eb** and **3fb** were obtained in similar yields, while a low yielding reaction was obtained from the primary alcohol counterpart. Curiously, both indolone- and fluorene-tethered TMS-alkynols **4h,i** reacted in a slightly different way than did alkynols **4a–g**, but their transformation into the corresponding products was clean. The initially obtained indolone- and fluorene-based α,β-unsaturated ketones **3hb** and **3ib** evolves under the reaction conditions to afford the allylic alcohol **6hb** and the β-alkoxy ketone **7ib**, respectively (Scheme 4). The formation of fluorene-derived adduct **7ib** must be ascribed to a Michael-type addition of the solvent to the initially obtained tetrasubstituted α,β-unsaturated ketone **3ib**, while the obtention of oxindole-derived adduct **6hb** deals with a 1,2-addition/isomerization sequence in putative ketone **3hb**. The lactam moiety should be responsible for the different evolution of ketone **3hb** in comparison with **3ib**. This general trend for indolone- and fluorene-derivatives was confirmed through the extension of the above reactions to various arenediazonium

Scheme 4. Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Alkynols 4 with Arenediazonium Salt 2b



salts, as summarized in Scheme 5. The exception was the fluorene-linked CF_3-substituted α,β-unsaturated ketone **3ig**.

Scheme 5. Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Alkynols 4h,i with Arenediazonium Salts 2e,g,h



Aiming to take advantage of the inert reactivity of the triisopropylsilyl-alkyne moiety under the current dual gold-photoredox catalytic conditions in comparison with its highly reactive trimethylsilyl-alkyne counterpart, we infer that the use of a mixed TMS/TIPS-diynol **4** as starting material should afford a conjugate enynone. Indeed, the photoreaction of 1-(triisopropylsilyl)-5-(trimethylsilyl)penta-1,4-diyn-3-ol **4j** produced good results and exquisite chemoselectivity in favor of the TMS-alkyne with the TIPS-alkyne remaining unaltered in (*E*)-1,2-bis(4-bromophenyl)-5-(triisopropylsilyl)pent-2-en-4-yn-1-one **3jb** (Scheme 6).[10]

Next, aiming to generate 2,3-diarylbenzofurans we moved to a different type of TMS-alkynol, namely, the 2-[(trimethylsilyl)-ethynyl]phenol **8**.[11] Surprisingly, the reaction of TMS-alkynol **8** with various arenediazonium salts **2** under the above optimized conditions using Gagosz's catalyst[12] generated mostly or exclusively the monoarylated 2-arylbenzofurans **9** (Scheme 7), depending on the amount (6 equiv or 1.3 equiv) of diazonium

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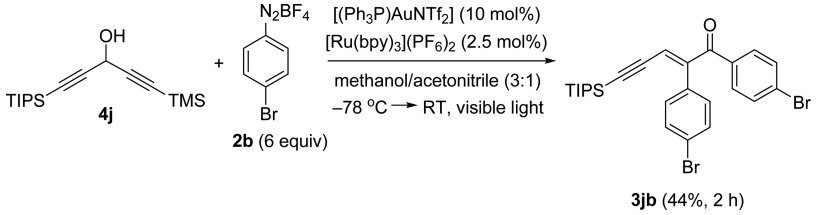
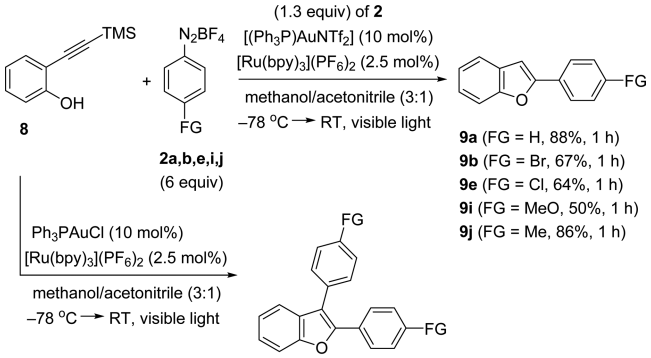
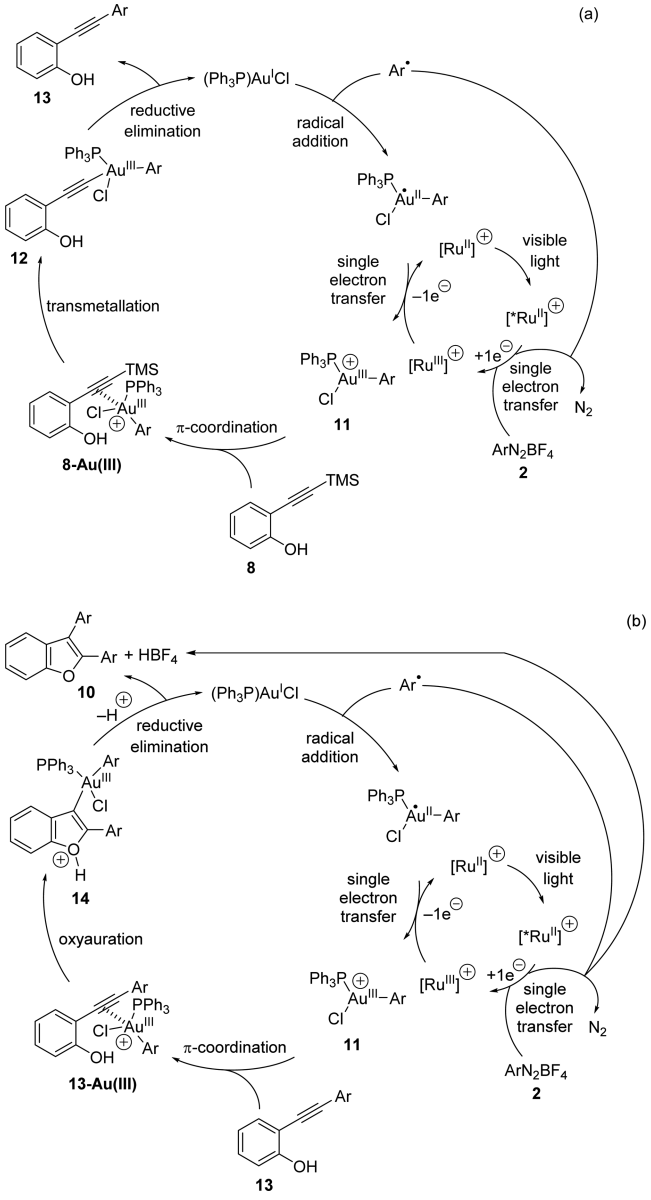
Scheme 6. Chemoselective Gold-Photoredox Cocatalyzed Domino C(sp) Arylation/Oxyarylation of Diynol 4j with Arenediazonium Salt 2b



Scheme 7. Gold-Photoredox Cocatalyzed C(sp) Arylation and Domino C(sp) Arylation/Oxyarylation of Alkynol 8 with Arenediazonium Salts 2a,b,e,i,j



Scheme 8. Mechanistic Outline for the Gold-Photoredox Cocatalyzed C(sp) Arylation and Domino C(sp) Arylation/Oxyarylation of Alkynol 8 with Arenediazonium Salts 2



salt **2**.[13] Interestingly, moving to Ph_3PAuCl under otherwise identical conditions allows introducing two aryl motifs in the skeleton of the benzofuran adduct, which grants a divergent preparation of both 2-arylbenzofurans **9** and 2,3-diarylbenzofurans **10** (Scheme 7). The superior performance of Ph_3PAuCl in comparison with $[(Ph_3P)AuNTf_2]$ pointed out to a competitive hydrofunctionalization which overrides the oxyarylation step for the Gagosz's catalyst case.[14] The initial event was the C(sp) arylation reaction of the TMS terminated alkyne, which is preferred over the further oxycyclization step under these dual gold/photoredox-catalyzed conditions.

A conceivable mechanistic proposal[15] that rationalizes the formation of adducts **10** is shown in Scheme 8. Initially, an aryl radical is formed from the corresponding arenediazonium salt **2** through a single electron transfer (SET) process involving both light and the photoredox catalyst. The so-generated highly reactive radical is added to the gold(I) complex, which after consecutive radical addition to the metallic center and single electron oxidation gives rise to arylgold(III) species **11**. Next, the TMS-terminated alkynol **8** comes into the gold-catalyzed cycle giving rise to the complex **8**-Au(III), which after Si–Au transmetalation generates gold acetylides **12**. Reductive elimination with concomitant aryl transfer delivers intermediate aryl alkynes **13** and releases the gold(I) precatalyst (Scheme 8a). The conversion of alkynes **13** into 2,3-diarylbenzofurans **10** again should require as first event the formation of arylgold(III) species **11** as above, followed by (a) alkyne activation through gold π-coordination, (b) 5-*endo* oxyauration, and (c) reductive elimination associated with deprotonation (Scheme 8b).

To add value to the proposed synthetic sequence and gain access to adducts bearing two different aryl groups, the crossover experiment of TMS-alkynol **4a** was designed with two similar arenediazonium salts, **2a** and **2b**. As expected, crossover products **4aab** and **4aba** together with adducts **4aa** and **4ab** were observed, supporting the formation of 3-aryl-1-phenylprop-2-yn-1-ol intermediates. In order to selectively

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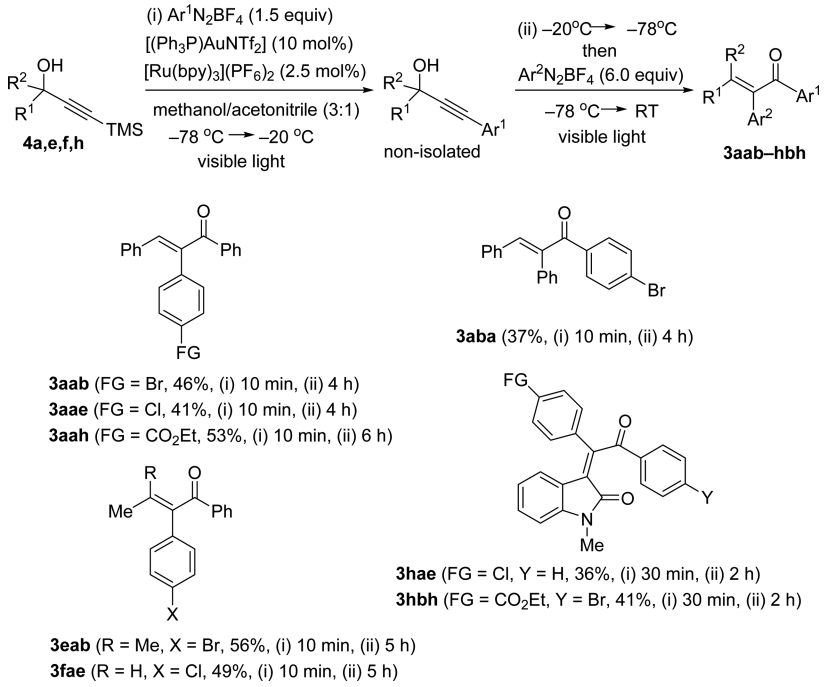
Scheme 9. Gold-Photoredox Cocatalyzed Domino Cross C(sp) Arylation/Oxyarylation of Alkynols 4a,e,f,h with Arenediazonium Salts 2a,b,e,h



obtain cross-adducts, this quickly and in situ generated aryl-1-phenylprop-2-yn-1-ols then should undergo a selective cross-oxyarylation with a different arenediazonium salt. After some experimentation, we managed to furnish cross-coupled adducts as exclusive products in one-pot when both 1.5 equiv of the first diazonium salt and temperature control were used. This cross sequence has a reasonable substrate scope and differently arylated α,β-unsaturated ketones were obtained (Scheme 9). In this case, α,β-unsaturated ketone-linked oxindoles **3hae** and **3hbh** were obtained as the sole reaction products.

CONCLUSIONS

In conclusion, the controlled preparation of polysubstituted α,β-unsaturated ketones and 2,3-diarylbenzofurans has been accomplished through light promoted dual gold-photoredox cocatalysis starting from 3-(trimethylsilyl)prop-2-yn-1-ols and 2-[(trimethylsilyl)ethynyl]phenol, respectively. The double arylation reaction was not effective using terminal alkynes or TIPS-terminated alkynes as precursors.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300, 500, or 700 MHz spectrometers. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), $CDCl_3$ (^{13}C, 76.9 ppm), and C_6D_6 (^{13}C, 128.4 ppm). Low- and high-resolution mass spectra were performed on a QTOF LC-MS spectrometer using the electrospray mode (ES) unless otherwise stated. All commercially available compounds were used without further purification. Flash chromatography was performed by using silica gel 60 (230−400 mesh) or neutral alumina. Products were identified by TLC (silica gel). UV light (λ = 254 nm) and a solution of phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) was used to develop the plates.

Alkynols 4a, 4b, 4d−g, 4i, 4j, 4a-TIPS and 8 Were Prepared by Known Literature Procedures.[16] *Procedure for the Preparation of Alkynol* ***4c.*** *n*-BuLi (1.4 mol, 2.5 M solution in hexane) was added to a solution of trimethylsilylacetylene (1.3 mol) in THF (2.1 mL) cooled at −78 °C. The mixture was allowed to warm to room temperature and it was stirred for 1 h at rt. The mixture was cooled at −78 °C and then it was added dropwise to a solution of the appropriate aldehyde (1.3 equiv) in THF (1.6 mL) at −78 °C. The reaction mixture was warmed up to room temperature and stirred overnight at rt, before being quenched with NH_4Cl (aq. sat.). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel gave analytically pure compound **4c**.

Alkynol ***4c.*** From 100 mg (0.74 mmol) of terephthalaldehyde, and after chromatography of the residue using hexanes/dichloromethane (1:1 → 0:1) as eluent, gave compound **4c** (72 mg, 42%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 10.0 (s, 1H), 7.89 (m, 2H), 7.71 (m, 2H), 5.53 (s, 1H), 2.75 (s, 1H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 192.0, 146.7, 136.1, 130.0 (2C), 127.1 (2C), 104.0, 92.4, 64.3, − 0.30 (3C); IR ($CHCl_3$, cm^{-1}): ν 3440, 2173, 1700; HRMS (ES): calcd for $C_{13}H_{15}O_2Si$ [M−H]$^+$: 231.0836; found: 231.0851.

Procedure for the Preparation of Alkynol ***4h.*** *n*-BuLi (1.4 mol, 2.5 M solution in hexane) was added to a solution of trimethylsilylacetylene (1.3 mol) in THF (2.1 mL) cooled at −78 °C. The mixture was allowed to warm to room temperature and it was stirred for 1 h at rt. The mixture was cooled at −78 °C and then a solution of the appropriate ketone (1.3 equiv) in THF (1.6 mL) was added dropwise. The reaction mixture was warmed up to room temperature and stirred overnight at rt, before being quenched with NH_4Cl (aq. sat.). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel gave analytically pure compound **4h**.

Alkynol ***4h.*** From 300 mg (1.86 mmol) of 1-methylisatin, and after chromatography of the residue using hexanes/ethyl acetate (8:2 → 1:1) as eluent, gave compound **4h** (301 mg, 62%) as a yellow solid; mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.54 (m, 1H), 7.37 (m, 1H), 7.14 (m, 1H), 6.84 (m, 1H), 3.21 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 173.6, 143.1, 130.4, 128.7, 124.6, 123.7, 108.7, 100.9, 92.1, 69.3, 26.6, 0.39 (3C); IR ($CHCl_3$, cm^{-1}): ν 3319, 2165, 1713; HRMS (ES): calcd for $C_{14}H_{18}NO_2Si$ [M +H]$^+$: 260.1101; found: 260.1093.

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*General Procedure for the Dual Gold-Photoredox 2-Fold Arylation Reaction of TMS-Alkynols **4a–j** and Diazonium Salts **2a–l**, Preparation of Diarylated α,β-Unsaturated Ketones **3aa–3jb**, Allylic Alcohols **6hb–6hh** and β-Alkoxy Ketones **7ib–7ih**.* In a Schlenk tube in the absence of light at −78 °C under argon atmosphere, [(Ph$_3$P)AuNTf$_2$] (10 mol%) and [Ru(bpy)$_3$](PF$_6$)$_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arene diazonium salt **2** (6.0 equiv) in a mixture of MeOH/MeCN (3:1, 5.0 mL). Then, a solution of the appropriate TMS-alkynol **4** (1.0 mmol) in MeOH/MeCN (3:1, 2.5 mL) was added dropwise and the reaction was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **3**, **6**, and **7** follow.

*Diarylated α,β-Unsaturated Ketone **3aa**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (1:1) as eluent, gave compound **3aa** (19 mg, 69%) as a colorless solid; mp 99–101 °C; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.89 (m, 2H), 7.50 (m, 3H), 7.29 (m, 9H), 7.12 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 197.6, 140.7, 140.2, 138.1, 136.4, 134.7, 132.1, 130.3 (2C), 129.7 (2C), 129.6 (2C), 128.9, 128.7 (2C), 128.3 (2C), 128.2 (2C), 127.9; IR (CHCl$_3$, cm^{-1}): ν 1652 (C═O); HRMS (ES): calcd for C$_{21}$H$_{17}$O [M+H]$^+$: 285.1274; found: 285.1275.

*Diarylated α,β-Unsaturated Ketone **3ab**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/acetate (95:5) as eluent, gave compound **3ab** (36 mg, 82%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.62 (m, 2H), 7.52 (m, 2H), 7.42 (m, 2H), 7.17 (m, 4H), 7.06 (m, 2H), 7.02 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 196.1, 141.3, 139.1, 136.7, 135.1, 134.1, 132.1 (2C), 131.7 (2C), 131.4 (2C), 131.2 (2C), 130.3 (2C), 129.4, 128.5 (2C), 127.3, 122.4; IR (CHCl$_3$, cm^{-1}): ν 1654; HRMS (ES): calcd for C$_{21}$H$_{15}$OBr$_2$ [M+H]$^+$: 440.9484; found: 440.9467.

*Diarylated α,β-Unsaturated Ketone **3ac**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (4:6) as eluent, gave compound **3ac** (19 mg, 61%) as a colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.89 (m, 2H), 7.23 (m, 6H), 7.10 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 196.0, 165.2 (d, J_{CF} = 254.0 Hz), 165.2 (d, J_{CF} = 247.7 Hz), 140.4, 139.4, 134.4, 134.1 (d, J_{CF} = 3.08 Hz), 132.3 (d, J_{CF} = 9.2 Hz, 2C), 132.2 (d, J_{CF} = 3.78 Hz), 131.5 (d, J_{CF} = 8.1 Hz, 2C), 130.3 (2C), 129.2, 128.4 (2C), 116.0 (d, J_{CF} = 21.5 Hz, 2C), 115.5 (d, J_{CF} = 21.8 Hz, 2C); ^{19}F NMR (282 MHz, CDCl$_3$, 25 °C): δ = −106.4 (s, 1F), −113.7 (s, 1F); IR (CHCl$_3$, cm^{-1}): ν 1654; HRMS (ES): calcd for C$_{21}$H$_{15}$OF$_2$ [M+H]$^+$: 321.1086; found: 321.1097.

*Diarylated α,β-Unsaturated Ketone **3ad**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/acetate (95:5) as eluent, gave compound **3ad** (20 mg, 37%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.82 (m, 2H), 7.70 (m, 2H), 7.54 (m, 2H), 7.22 (m, 4H), 7.10 (m, 2H), 7.01 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 196.3, 141.3, 139.2, 138.0 (2C), 137.7 (2C), 137.2, 135.7, 134.2, 131.6 (2C), 131.1 (2C), 130.3 (2C), 129.4, 128.5 (2C), 99.9, 94.1; IR (CHCl$_3$, cm^{-1}): ν 1655; HRMS (ES): calcd for C$_{21}$H$_{14}$OI$_2$Na [M+Na]$^+$: 558.9026; found: 558.9021.

*Diarylated α,β-Unsaturated Ketone **3ae**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (8:2) as eluent, gave compound **3ae** (27 mg, 77%) as a colorless solid; mp 124–126 °C; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.79 (m, 2H), 7.44 (m, 2H), 7.35 (m, 2H), 7.23 (m, 6H), 7.11 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 196.0, 141.2, 139.2, 138.7, 136.2, 134.6, 134.2, 134.1, 131.1 (4C), 130.3 (2C), 129.4, 129.1 (2C), 128.7 (2C), 128.4 (2C); IR (CHCl$_3$, cm^{-1}): ν 1652; HRMS (ES): calcd for C$_{21}$H$_{15}$OCl$_2$ [M+H]$^+$: 353.0494; found: 353.0488.

*Diarylated α,β-Unsaturated Ketone **3af**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/acetate (8:2) as eluent, gave compound **3af** (10 mg, 26%) as a yellow oil; ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C) δ: 8.36 (m, 2H), 8.27 (m, 2H), 7.97 (m, 2H), 7.48 (m, 2H), (s, 1H), 7.33 (m, 1H,), 7.25 (m, 2H), 7.25 (m, 2H), 7.05 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C) δ: 194.7, 149.8, 147.7, 145.2, 143.3, 142.6, 138.0, 133.1, 131.0 (2C), 130.6 (2C), 130.5, 130.3 (2C), 128.8 (2C), 124.1 (2C), 123.7 (2C); IR (CHCl$_3$, cm^{-1}): ν 1647, 1519, 1347; HRMS (ES): calcd for C$_{21}$H$_{15}$O$_5$N$_2$ [M+H]$^+$: 375.0975; found: 375.0965.

*Diarylated α,β-Unsaturated Ketone **3ag**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (8:2 → 7:3) as eluent, gave compound **3ag** (7 mg, 17%) as a colorless oil; ^{1}H NMR (700 MHz, CDCl$_3$, 25 °C) δ: 7.94 (m, 2H), 7.76 (m, 2H), 7.66 (m, 2H), 7.42 (m, 2H), 7.36 (s, 1H), 7.30 (m, 1H), 7.23 (m, 2H), 7.06 (m, 2H); ^{13}C NMR (175 MHz, CDCl$_3$, 25 °C) δ: 195.9, 143.2, 141.2, 139.7, 138.9, 133.7, 133.6 (q, J_{CF} = 32.6 Hz), 130.5 (2C), 130.3 (q, J_{CF} = 32.3 Hz), 130.2 (2C), 129.9, 129.8 (2C), 128.6 (2C), 125.8 (2C), 125.5 (2C), 124.0 (q, J_{CF} = 271.9 Hz), 123.6 (q, J_{CF} = 272.7 Hz); ^{19}F NMR (282 MHz, CDCl$_3$, 25 °C): δ = −62.9 (s, 3F), − 63.3 (s, 3F); IR (CHCl$_3$, cm^{-1}): ν 1659, 1325; HRMS (ES): calcd for C$_{23}$H$_{15}$OF$_6$ [M+H]$^+$: 421.1022; found: 421.1006.

*Diarylated α,β-Unsaturated Ketone **3ah**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (4:6) as eluent, gave compound **3ah** (24 mg, 57%) as a colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 8.12 (m, 2H), 8.05 (m, 2H), 7.85 (m, 2H), 7.36 (m, 3H), 7.23 (m, 3H), 7.06 (m, 2H), 4.40 (m, 4H), 1.42 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 196.4, 166.3, 165.8, 142.7, 141.8, 140.1, 139.6, 134.0, 133.4, 130.5 (2C), 130.0 (2C), 129.9 (2C), 129.7, 129.5 (2C), 129.3 (2C), 128.5 (2C), 61.4, 61.1, 14.4, 14.3; IR (CHCl$_3$, cm^{-1}): ν 1719, 1654; HRMS (ES): calcd for C$_{27}$H$_{25}$O$_5$ [M+H]$^+$: 429.1697; found: 429.1703.

*Diarylated α,β-Unsaturated Ketone **3ak**.* From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (1:1) as eluent, gave compound **3ak** (33 mg, 75%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.98 (m, 1H), 7.75 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 7.45 (m, H), 7.36 (m, H), 7.27 (m, 2H), 7.45 (m, 4H), 7.09 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 195.5, 142.3, 139.9, 138.7, 138.1, 135.1, 133.9, 132.5, 132.4, 131.2, 130.5 (2C), 130.4, 129.9, 129.7, 128.5 (2C), 128.4, 128.2, 122.8, 122.7; IR (CHCl$_3$, cm^{-1}): ν 1654; HRMS (ES): calcd for C$_{21}$H$_{15}$OBr$_2$ [M+H]$^+$: 440.9484; found: 440.9483.

*Diarylated α,β-Unsaturated Ketone **3bb**.* From 24 mg (0.10 mmol) of TMS-alkynol **4b**, and after chromatography of the residue using hexanes/toluene (75:15) as eluent, gave compound **3bb** (30 mg, 64%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 7.69 (m, 2H), 7.60 (m, 2H), 7.50 (m, 2H), 7.20 (m, 3H), 7.13 (m, 2H), 7.04 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 195.7, 139.7, 139.5, 136.4, 135.3, 134.7, 132.6, 132.2 (2C), 131.7 (2C), 131.5 (2C), 131.3 (2C), 131.2 (2C), 128.8 (2C), 127.5, 122.6; IR (CHCl$_3$, cm^{-1}): ν 1655; HRMS (ES): calcd for C$_{21}$H$_{14}$OBr$_2$Cl [M+H]$^+$: 474.9094; found: 474.9109.

*Diarylated α,β-Unsaturated Ketone **3cb**.* From 23 mg (0.10 mmol) of TMS-alkynol **4c**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **3cb** (35 mg, 53%) as a colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ: 9.97 (s, 1H), 7.73 (m, 4H), 7.61 (m, 2H), 7.50 (m, 2H), 7.27 (m, 2H), 7.24 (s, 1H), 7.13 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C) δ: 195.5, 191.4, 141.7, 140.3, 138.1, 136.1, 135.9, 134.3, 132.3 (2C), 131.8 (2C), 131.3 (2C), 131.2 (2C), 130.6 (2C), 129.6 (2C), 127.9, 122.9; IR (CHCl$_3$, cm^{-1}): ν 1699, 1655; HRMS (ES): calcd for C$_{22}$H$_{15}$Br$_2$O$_2$ [M+H]$^+$: 468.9433; found: 468.9442.

*Diarylated α,β-Unsaturated Ketone **3db**.* From 21 mg (0.10 mmol) of TMS-alkynol **4d**, and after chromatography of the residue using hexanes/toluene (6:4) as eluent, gave compound **3db** (30 mg, 67%) as a yellow oil; ^{1}H NMR (300 MHz, C$_6$D$_6$, 25 °C) δ: 7.49–7.43 (m, 5H), 7.28 (d, 2H, J = 8.4 Hz), 7.03 (d, 2H, J = 8.4 Hz), 6.72 (dd, 1H, J = 13.8 Hz, J = 5.1 Hz), 6.55 (dd, 1H, J = 5.1 Hz, J = 3.7 Hz); ^{13}C

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NMR (75 MHz, C_6D_6, 25 °C) δ: 193.7, 138.5 (2C), 137.6, 136.6, 135.1, 133.8, 132.7 (2C), 132.3 (2C), 131.8 (2C), 131.2 (2C), 131.1, 126.9, 126.8, 123.3; IR ($CHCl_3$, cm^{-1}): ν 1689; HRMS (ES): calcd for $C_{19}H_{13}Br_2OS$ $[M+H]^+$: 446.9048; found: 446.9041.

Diarylated α,β-Unsaturated Ketone ***3eb***. From 16 mg (0.10 mmol) of TMS-alkynol **4e**, and after chromatography of the residue using toluene as eluent, gave compound **3eb** (28 mg, 71%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.79 (d, 2H, J = 8.8 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.7 Hz), 7.15 (d, 2H, J = 8.7 Hz), 1.87 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 197.3, 137.2, 135.8, 135.5, 135.2, 132.1 (2C), 131.7 (2C), 131.1 (2C), 130.9 (2C), 128.6, 121.5, 22.7, 21.4; IR ($CHCl_3$, cm^{-1}): ν 1658; HRMS (ES): calcd for $C_{17}H_{15}Br_2O$ $[M+H]^+$: 392.9484; found: 392.9498.

Diarylated α,β-Unsaturated Ketone ***3fb***. From 14 mg (0.10 mmol) of TMS-alkynol **4f**, and after chromatography of the residue using hexanes/toluene (6:4) as eluent, gave compound **3fb** (24 mg, 63%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.63−7.57 (m, 4H), 7.53 (d, 2H, J = 8.6 Hz), 7.12 (d, 2H, J = 8.6 Hz), 6.63 (q, 1H, J = 7.3 Hz), 1.88 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 195.6, 141.6, 141.0, 136.9, 134.3, 131.6 (2C), 131.6 (2C), 131.3 (2C), 131.1 (2C), 127.0, 121.9, 15.7; IR ($CHCl_3$, cm^{-1}): ν 1655; HRMS (ES): calcd for $C_{16}H_{13}Br_2O$ $[M+H]^+$: 378.9328; found: 378.9339.

Diarylated α,β-Unsaturated Ketone ***3gb***. From 13 mg (0.10 mmol) of TMS-alkynol **4g**, and after chromatography of the residue using toluene as eluent, gave compound **3gb** (9 mg, 23%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.74 (d, 2H, J = 8.6 Hz), 7.59 (d, 2H, J = 8.6 Hz), 7.49 (d, 2H, J = 8.6 Hz), 7.28 (d, 2H, J = 8.6 Hz), 6.10 (s, 1H), 5.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 195.9, 146.9, 136.6, 136.5, 131.9 (2C), 131.4 (2C), 128.7 (2C), 128.5, 122.9, 122.2; IR ($CHCl_3$, cm^{-1}): ν 1685; HRMS (ES): calcd for $C_{15}H_{11}Br_2O$ $[M+H]^+$: 364.9171; found: 364.9173.

Diarylated α,β-Unsaturated Ketone ***3ig***. From 28 mg (0.10 mmol) of TMS-alkynol **4i**, and after chromatography of the residue using hexanes/toluene (8:2) as eluent, gave compound **3ig** (24 mg, 49%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.27 (d, 2H, J = 8.2 Hz), 7.77−7.69 (m, 8H), 7.37−7.33 (m, 2H), 7.20 (d, 1H, J = 8.0 Hz), 7.06−7.00 (m, 2H), 6.67 (d, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 196.0, 141.4, 140.9, 139.3, 137.6, 137.3, 136.4, 136.4, 135.8, 135.4, 131.1, 130.3 (2C), 129.7 (2C), 129.6, 129.5, 127.5, 127.2, 126.4 (2C), 126.3 (2C), 125.3, 124.9, 123.8 (q, J_{CF} = 270 Hz), 123.4 (q, J_{CF} = 270 Hz), 120.0, 119.9; ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −63.0 (s, 3F), − 63.5 (s, 3F); IR ($CHCl_3$, cm^{-1}): ν 1643, 1612; HRMS (ES): calcd for $C_{29}H_{17}F_6O$ $[M+H]^+$: 495.1178; found: 495.1184.

Diarylated α,β-Unsaturated Ketone ***3jb***. From 31 mg (0.10 mmol) of TMS-alkynol **4j**, and after chromatography of the residue using hexanes/toluene (8:2) as eluent, gave compound **3jb** (24 mg, 44%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.65 (m, 2H), 7.57 (m, 2H), 7.48 (s, 4H), 6.35 (s, 1H), 1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 195.1, 148.1, 135.8, 134.0, 131.8 (2C), 131.4 (2C), 131.3 (2C), 130.8 (2C), 128.1, 122.9, 118.7, 106.8, 102.6, 18.5 (6C), 11.2 (3C); IR ($CHCl_3$, cm^{-1}): ν 1662; HRMS (ES): calcd for $C_{26}H_{31}OBr_2Si$ $[M+H]^+$: 545.0505; found: 545.0469.

Diarylated α,β-Unsaturated Ketone ***6hb***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **6hb** (30 mg, 57%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.33−7.26 (m, 6H), 7.06 (d, 1H, J = 7.1 Hz), 7.02 (d, 2H, J = 8.2 Hz), 6.92 (d, 2H, J = 8.2 Hz), 6.84 (d, 1H, J = 7.1 Hz), 3.73 (s, 1H), 3.25 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 177.0, 153.6, 143.9, 134.2, 133.7 (2C), 132.0, 131.5 (2C, 131.4, 131.2 (2C), 131.0 (2C), 129.6, 124.0, 123.8, 122.9, 122.6, 121.6, 108.2, 77.0, 57.1, 26.3; IR ($CHCl_3$, cm^{-1}): ν 3360, 1610; HRMS (ES): calcd for $C_{24}H_{19}Br_2NNaO_3$ $[M+Na]^+$: 549.9624; found: 549.9632.

Diarylated α,β-Unsaturated Ketone ***6he***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **6he** (20 mg, 45%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.33 (td, 1H, J = 7.1 Hz, J = 1.3 Hz), 7.28 (d, 1H, J = 7.1 Hz), 7.15 (d, 2H, J = 8.3 Hz), 7.12 (d, 2H, J = 8.2 Hz), 7.08 (d, 2H, J = 8.2 Hz), 7.04 (d, 1H, J = 7.2 Hz), 6.99 (d, 2H, J = 8.3 Hz), 6.84 (d, 1H, J = 7.1 Hz), 3.76 (s, 1H), 3.25 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 177.0, 153.6, 143.9, 134.2, 133.9, 133.3 (2C), 133.3, 131.5, 131.4, 131.2 (2C), 129.5, 128.2 (2C), 128.0 (2C), 123.8, 123.8, 122.9, 108.2, 77.0, 57.2, 26.2; IR ($CHCl_3$, cm^{-1}): ν 3363, 1611; HRMS (ES): calcd for $C_{24}H_{19}Cl_2NNaO_3$ $[M+Na]^+$: 462.0634; found: 462.0636.

Diarylated α,β-Unsaturated Ketone ***6hg***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **6hg** (18 mg, 36%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.45 (d, 2H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.2 Hz), 7.35 (t, 1H, J = 7.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.26 (d, 1H, J = 7.1 Hz), 7.16 (d, 2H, J = 8.2 Hz), 7.07 (t, 1H, J = 7.2 Hz), 6.87 (d, 1H, J = 7.4 Hz), 3.54 (s, 1H), 3.28 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 176.9, 153.4, 144.0, 139.0, 136.6, 132.5 (2C), 131.2, 130.3, 129.8 (2C), 129.4, 125.2, 125.0 (2C), 124.7 (2C), 123.9 (q, J_{CF} = 270 Hz, CF_3), 123.8, 123.4 (q, J_{CF} = 270 Hz, CF_3), 123.0 (2C), 108.4, 77.0, 57.3, 26.3; ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −62.9 (s, 3F), − 63.2 (s, 3F); IR ($CHCl_3$, cm^{-1}): ν 3365, 1614; HRMS (ES): calcd for $C_{26}H_{20}F_6NO_3$ $[M+H]^+$: 508.1342; found: 508.1357.

Diarylated α,β-Unsaturated Ketone ***6hh***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **6hh** (25 mg, 48%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.82−7.76 (m, 4H), 7.33−7.25 (m, 2H), 7.21 (d, 2H, J = 8.3 Hz), 7.11 (d, 2H, J = 8.2 Hz), 7.03 (t, 1H, J = 7.4 Hz), 6.83 (d, 1H, J = 7.1 Hz), 4.33−4.28 (m, 4H), 3.24 (s, 3H), 3.14 (s, 3H), 1.32−1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 177.0, 166.2, 165.8, 153.8, 143.9, 140.2, 137.5, 131.0 (2C), 131.2, 130.2, 129.8 (2C), 129.5, 129.2, 129.0 (2C), 128.8 (2C), 125.1, 124.0, 122.8, 108.3, 77.1, 61.0, 61.0 (2C), 57.2, 26.2, 14.2 (2C); IR ($CHCl_3$, cm^{-1}): ν 3368, 1680, 1614; HRMS (ES): calcd for $C_{30}H_{29}NNaO_7$ $[M+Na]^+$: 538.1836; found: 538.1833.

Diarylated α,β-Unsaturated Ketone ***7ib***. From 28 mg (0.10 mmol) of TMS-alkynol **4i**, and after chromatography of the residue using hexanes/toluene (8:2) as eluent, gave compound **7ib** (32 mg, 59%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.78−7.72 (m, 3H), 7.54−7.50 (m, 4H), 7.37−7.25 (m, 5H), 7.14 (d, 2H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 5.42 (s, 1H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 196.6, 143.7, 142.3, 141.6 (2C), 141.3, 137.2, 132.4, 132.0 (2C), 131.7 (2C), 130.6 (2C), 130.0 (2C), 129.3, 127.9, 127.2, 127.1, 126.4, 124.6, 121.8, 119.9, 119.7, 90.1, 59.7, 51.5; IR ($CHCl_3$, cm^{-1}): ν 1655; HRMS (ES): calcd for $C_{28}H_{20}Br_2NaO_2$ $[M+Na]^+$: 570.9704; found: 570.9714.

Diarylated α,β-Unsaturated Ketone ***7ie***. From 28 mg (0.10 mmol) of TMS-alkynol **4i**, and after chromatography of the residue using hexanes/toluene (6:4) as eluent, gave compound **7ie** (27 mg, 60%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.78 (d, 2H, J = 8.4 Hz), 7.68 (d, 1H, J = 7.3 Hz), 7.43 (d, 2H, J = 7.3 Hz), 7.18−7.30 (m, 7H), 6.90 (d, 2H, J = 8.4 Hz), 6.84 (d, 2H, J = 8.4 Hz), 5.36 (s, 1H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 196.5, 143.7, 142.3, 141.7, 141.3, 139.2, 136.7, 133.5, 132.0, 131.7 (2C), 130.0 (2C), 129.3 (2C), 128.8 (2C), 127.7 (2C), 127.2, 127.2, 125.6, 124.6, 119.9, 119.8, 90.2, 59.7, 51.6; IR ($CHCl_3$, cm^{-1}): ν 1644; HRMS (ES): calcd for $C_{28}H_{20}Cl_2NaO_2$ $[M+Na]^+$: 481.0732; found: 481.0747.

Diarylated α,β-Unsaturated Ketone ***7ih***. From 28 mg (0.10 mmol) of TMS-alkynol **4i**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **7ih** (23 mg, 44%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.96 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz), 7.69 (d, 2H, J = 7.0 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.18−7.30 (m, 5H), 6.98 (d, 2H, J = 8.2 Hz), 5.51 (s, 1H), 4.31 (q, 2H, J = 7.0 Hz), 4.22 (q, 2H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.0 Hz), 1.27 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 197.2, 166.4, 165.7, 143.5, 142.2, 141.8, 141.6, 141.3, 138.4, 133.8, 130.4 (2C), 129.6 (2C), 129.5, 129.4 (2C), 128.7 (2C), 128.4 (2C), 127.3, 127.2, 126.5, 124.6, 119.9, 119.8, 90.3, 60.9, 60.8, 60.8, 51.5, 14.3 (2C); IR ($CHCl_3$, cm^{-1}): ν

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1660; HRMS (ES): calcd for $C_{34}H_{31}O_6$ $[M+H]^+$: 535.2115; found: 535.2135.

*General Procedure for the Dual Gold-Photoredox Arylation/Oxyarylation Reaction of **2**-[(Trimethylsilyl)ethynyl]phenol **8** and Diazonium Salts **2**, Preparation of **2**-Arylbenzofurans **9**.* In a Schlenk tube in the absence of light at −78 °C under argon atmosphere, $[(Ph_3P)AuNTf_2]$ (10 mol%) and $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arene diazonium salt **2** (1.3 equiv) in a mixture of MeOH/MeCN (3:1, 5.0 mL). Then, a solution of TMS-alkynol **8** (1.0 mmol) in MeOH/MeCN (3:1, 2.5 mL) was added dropwise and the reaction was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **9** follow.

*2-Arylbenzofuran **9a**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **9a** (17 mg, 88%) as a colorless solid; mp 120−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.89 (d, 1H, J = 7.6 Hz), 7.61 (dd, 1H, J = 8.5 Hz, J = 1.3 Hz), 7.55 (d, 1H, J = 7.6 Hz), 7.50−7.45 (m, 2H), 7.38 (d, 1H, J = 7.2 Hz), 7.35−7.23 (m, 3H), 7.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 155.9, 154.9, 130.5, 129.2, 128.8 (2C), 128.6, 124.9 (2C), 124.3, 122.9, 120.9, 115.2, 101.3; IR ($CHCl_3$, cm^{-1}): ν 1477, 1445; HRMS (ES): calcd for $C_{14}H_{11}O$ $[M+H]^+$: 195.0810; found: 195.0828.

*2-Arylbenzofuran **9b**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **9b** (16 mg, 67%) as a colorless solid; mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.72 (d, 2H, J = 8.5 Hz), 7.59−7.56 (m, 3H), 7.51 (d, 1H, J = 7.6 Hz), 7.33−7.21 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.8, 150.6, 131.9 (2C), 129.3, 128.9, 126.3 (2C), 124.5, 123.0, 122.4, 121.0, 111.1, 101.8; IR ($CHCl_3$, cm^{-1}): ν 1479, 1447; HRMS (ES): calcd for $C_{14}H_{10}BrO$ $[M+H]^+$: 272.9909; found: 272.9918.

*2-Arylbenzofuran **9e**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **9e** (15 mg, 64%) as a colorless solid; mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.80 (d, 2H, J = 8.4 Hz), 7.61−7.52 (m, 2H), 7.43 (d, 2H, J = 8.4 Hz), 7.34−7.22 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.9, 154.8, 134.3 (2C), 129.1 (2C), 129.0, 128.2 (2C), 124.6, 123.1, 121.0, 112.2, 101.8; IR ($CHCl_3$, cm^{-1}): ν 1480, 1448; HRMS (ES): calcd for $C_{14}H_{10}ClO$ $[M+H]^+$: 229.0415; found: 229.0424.

*2-Arylbenzofuran **9i**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **9i** (12 mg, 50%) as a colorless solid; mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.81 (d, 2H, J = 8.4 Hz), 7.58−7.56 (m, 2H), 7.28−7.20 (m, 2H), 6.99 (d, 2H, J = 8.4 Hz), 6.90 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 160.0, 156.1, 154.7, 129.5, 126.4 (2C), 123.8, 123.4, 122.8, 120.6, 114.3 (2C), 110.0, 99.70, 55.4; IR ($CHCl_3$, cm^{-1}): ν 1475, 1445; HRMS (ES): calcd for $C_{15}H_{13}O_2$ $[M+H]^+$: 225.0910; found: 225.0909.

*2-Arylbenzofuran **9j**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **9j** (18 mg, 86%) as a colorless solid; mp 129−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.78 (d, 2H, J = 7.6 Hz), 7.59 (d, 1H, J = 7.6 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.29−7.24 (m, 4H), 6.99 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 156.5, 155.2, 139.0, 129.9 (2C), 128.2, 125.3 (2C), 124.4, 123.3, 121.1, 111.5, 101.0, 21.8; IR ($CHCl_3$, cm^{-1}): ν 1485, 1443; HRMS (ES): calcd for $C_{15}H_{13}O$ $[M+H]^+$: 209.0961; found: 209.0952.

*General Procedure for the Dual Gold-Photoredox 2-Fold Arylation/Oxyarylation Reaction of **2**-[(Trimethylsilyl)ethynyl]-phenol **8** and Diazonium Salts **2**, Preparation of **2,3**-Diarylbenzofurans **10**.* In a Schlenk tube in the absence of light at −78 °C under argon atmosphere, Ph_3PAuCl (10 mol%) and $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arene diazonium salt **2** (6.0 equiv) in a mixture of MeOH/MeCN (3:1, 5.0 mL). Then, a solution of TMS-alkynol **8** (1.0 mmol) in MeOH/MeCN (3:1, 2.5 mL) was added dropwise and the reaction was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **10** follow.

*2,3-Diarylbenzofuran **10a**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **10a** (23 mg, 83%) as a colorless solid; mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.68 (dd, 2H, J = 8.1 Hz, J = 2.5 Hz), 7.58 (d, 1H, J = 8.1 Hz), 7.57−7.45 (m, 6H), 7.43−7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.0, 150.4, 133.3, 130.5, 130.2, 129.8 (2C), 129.0 (2C), 128.4 (2C), 128.4, 127.5, 127.0 (2C), 125.1, 122.8, 120.0, 117.4, 111.0; IR ($CHCl_3$, cm^{-1}): ν 1495, 1453; HRMS (ES): calcd for $C_{20}H_{15}O$ $[M+H]^+$: 271.1117; found: 271.1127.

*2,3-Diarylbenzofuran **10b**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **10b** (29 mg, 69%) as a colorless solid; mp 116−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.62 (d, 2H, J = 8.0 Hz), 7.58−7.46 (m, 6H), 7.39−7.35 (m, 3H), 7.30−7.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.0, 149.4, 132.4 (2C), 131.8 (2C), 131.4, 131.3 (2C), 129.5, 129.3, 128.4 (2C), 125.1, 123.3, 122.8, 122.0, 119.8, 116.7, 111.2; IR ($CHCl_3$, cm^{-1}): ν 1496, 1450; HRMS (ES): calcd for $C_{20}H_{13}Br_2O$ $[M+H]^+$: 426.9328; found: 426.9344.

*2,3-Diarylbenzofuran **10e**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **10e** (19 mg, 56%) as a colorless solid; mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.51−7.46 (m, 3H), 7.40−7.35 (m, 5H), 7.31−7.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 154.0, 149.7, 134.5, 133.8, 131.1, 131.0 (2C), 129.4, 129.4 (2C), 128.4 (2C), 128.3 (2C), 125.2, 123.3, 120.0, 116.8, 111.3; IR ($CHCl_3$, cm^{-1}): ν 1497, 1451; HRMS (ES): calcd for $C_{20}H_{13}Cl_2O$ $[M+H]^+$: 339.0343; found: 339.0327.

*2,3-Diarylbenzofuran **10i**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **10i** (7 mg, 21%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.61 (d, 2H, J = 8.5 Hz), 7.55−7.44 (m, 2H), 7.43 (d, 2H, J = 8.2 Hz), 7.22−7.20 (m, 2H), 7.01 (d, 2H, J = 8.2 Hz), 6.86 (d, 2H, J = 8.2 Hz), 3.90 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 159.6, 159.0, 153.8, 150.5, 130.9 (2C), 130.6, 128.4 (2C), 125.2, 124.2, 123.5, 123.2, 119.7, 115.7, 114.5 (2C), 113.9 (2C), 110.9, 55.3; IR ($CHCl_3$, cm^{-1}): ν 1490, 1450; HRMS (ES): calcd for $C_{22}H_{19}O_3$ $[M+H]^+$: 331.1328; found: 331.1326.

*2,3-Diarylbenzofuran **10j**.* From 19 mg (0.10 mmol) of TMS-alkynol **8**, and after chromatography of the residue using hexanes as eluent, gave compound **10j** (20 mg, 66%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.58 (d, 2H, J = 8.5 Hz), 7.52−7.50 (m, 2H), 7.41 (d, 2H, J = 8.5 Hz), 7.36−7.22 (m, 4H), 7.15 (d, 2H, J = 8.4 Hz), 2.46 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 153.8, 150.7, 138.3, 137.3, 130.4, 129.9, 129.7 (2C), 129.5 (2C), 129.0 (2C), 128.0, 126.9 (2C), 124.4, 122.8, 119.9, 116.8, 111.0, 21.4 (2C); IR ($CHCl_3$, cm^{-1}): ν 1498, 1448; HRMS (ES): calcd for $C_{22}H_{19}O$ $[M+H]^+$: 299.1430; found: 299.1416.

*General Procedure for the Dual Gold-Photoredox Cross Double Arylation Reaction of TMS-Alkynols **4** and Diazonium Salts **2**, Preparation of Crossed-Diarylated α,β-Unsaturated Ketones **3aab**−**3hbh**.* In a Schlenk tube in the absence of light at −78 °C under argon atmosphere, $[(Ph_3P)AuNTf_2]$ (10 mol%) and $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the first arene diazonium salt **2** (1.5 equiv) in a mixture of MeOH/MeCN (3:1, 4.0 mL). Then, a solution of the appropriate TMS-alkynol **4** (1.0 mmol) in MeOH/MeCN (3:1, 1.5 mL) was added dropwise and the reaction was stirred at −78 °C for 5 min. The reaction mixture was then warmed to −20 °C and stirred under irradiation from visible light

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source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC, typically 20 min), the reaction mixture was cooled at −78 °C and protected from the light. Then, a solution of the second arene diazonium salt **2** (6.0 equiv) in a mixture of MeOH/MeCN (3:1, 2.5 mL) was added, and the reaction was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of crossed adducts **3** follow.

Diarylated α,β-Unsaturated Ketone ***3aab***. From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (7:3) as eluent, gave compound **3aab** (16 mg, 46%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.85 (m, 2H), 7.52 (m, 6H), 7.20 (m, 5H), 7.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 197.2, 141.0, 139.5, 137.9, 135.4, 134.4, 132.3, 132.0 (2C), 131.5 (2C), 130.3 (2C), 129.7 (2C), 129.2, 128.4 (2C), 128.3 (2C), 122.2; IR ($CHCl_3$, cm^{-1}): ν 1653; HRMS (ES): calcd for $C_{21}H_{16}OBr$ $[M+H]^+$: 363.0379; found: 363.0376.

Diarylated α,β-Unsaturated Ketone ***3aae***. From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (7:3) as eluent, gave compound **3aae** (13 mg, 41%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.86 (m, 2H), 7.57 (m, 1H), 7.47 (m, 3H), 7.35 (m, 2H), 7.24 (m, 5H), 7.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 197.3, 141.1, 139.5, 138.0, 134.9, 134.5, 134.0, 132.3, 131.2 (2C), 130.3 (2C), 129.8 (2C), 129.2, 129.1 (2C), 128.5 (2C), 128.4 (2C); IR ($CHCl_3$, cm^{-1}): ν 1654; HRMS (ES): calcd for $C_{21}H_{16}OCl$ $[M+H]^+$: 319.0884; found: 319.0899.

Diarylated α,β-Unsaturated Ketone ***3aah***. From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (6:4) as eluent, gave compound **3aah** (19 mg, 53%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.05 (m, 2H), 7.87 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 7.38 (m, 2H), 7.33 (s, 1H), 7.21 (m, 3H), 7.08 (m, 2H), 4.39 (q, 4H, J = 7.1), 1.41 (m, 3H, J = 7.1); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 197.0, 166.4, 141.4, 141.3, 139.8, 137.9, 134.3, 132.3, 130.3 (2C), 130.0 (2C), 129.9, 129.8 (2C), 129.7 (2C), 129.3, 128.4 (2C), 128.6 (2C), 61.0, 14.3; IR ($CHCl_3$, cm^{-1}): ν 1717, 1654; HRMS (ES): calcd for $C_{24}H_{21}O_3$ $[M+H]^+$: 357.1485; found: 357.1499.

Diarylated α,β-Unsaturated Ketone ***3aba***. From 20 mg (0.10 mmol) of TMS-alkynol **4a**, and after chromatography of the residue using hexanes/toluene (7:3) as eluent, gave compound **3aba** (13 mg, 37%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.72 (m, 2H), 7.58 (m, 2H), 7.35 (m, 3H), 7.22 (m, 6H), 7.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 196.4, 140.5, 140.4, 136.9, 136.2, 134.6, 131.6 (2C), 131.3 (2C), 130.4 (2C), 129.6 (2C), 129.1, 128.9 (2C), 128.3 (2C), 128.1, 127.1; IR ($CHCl_3$, cm^{-1}): ν 1657; HRMS (ES): calcd for $C_{21}H_{16}OBr$ $[M+H]^+$: 363.0379; found: 363.0379.

Diarylated α,β-Unsaturated Ketone ***3eab***. From 16 mg (0.10 mmol) of TMS-alkynol **4e**, and after chromatography of the residue using hexanes/toluene (7:3) as eluent, gave compound **3eab** (17 mg, 56%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.95 (m, 2H), 7.53 (m, 1H), 7.43 (m, 4H), 7.19 (m, 2H), 1.87 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 198.4, 136.7, 136.3, 136.0, 135.6, 133.3, 131.5 (2C), 130.9 (2C), 129.7 (2C), 128.7 (2C), 121.3, 22.6, 21.3; IR ($CHCl_3$, cm^{-1}): ν 1662; HRMS (ES): calcd for $C_{17}H_{16}OBr$ $[M+H]^+$: 315.0379; found: 315.0390.

Diarylated α,β-Unsaturated Ketone ***3fae***. From 15 mg (0.10 mmol) of TMS-alkynol **4f**, and after chromatography of the residue using hexanes/toluene (7:3) as eluent, gave compound **3fae** (12 mg, 49%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 7.75 (m, 2H), 7.53 (m, 1H), 7.40 (m, 4H), 7.21 (m, 2H), 6.63 (q, 1H, J = 7.1 Hz), 1.88 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 196.9, 141.8, 140.6, 138.2, 134.1, 133.5, 132.0, 131.0 (2C), 129.5 (2C), 128.5 (2C), 128.2 (2C), 15.6; IR ($CHCl_3$, cm^{-1}): ν 1656; HRMS (ES): calcd for $C_{16}H_{14}OCl$ $[M+H]^+$: 257.0728; found: 257.0721.

Diarylated α,β-Unsaturated Ketone ***3hae***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **3hae** (13 mg, 36%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.04 (m, 2H), 7.56 (m, 3H), 7.45 (m, 4H), 7.31 (m, 1H), 7.00 (m, 1H), 6.84 (m, 2H), 3.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 195.8, 166.3, 147.6, 145.0, 136.0, 135.2, 133.5, 132.2, 130.6, 129.7 (2C), 129.6 (2C), 129.0 (2C), 128.8 (2C), 126.7, 123.2, 122.1, 120.4, 108.5, 26.0; IR ($CHCl_3$, cm^{-1}): ν 1709, 1669; HRMS (ES): calcd for $C_{23}H_{17}ClNO_2$ $[M+H]^+$: 374.0942; found: 374.0929.

Diarylated α,β-Unsaturated Ketone ***3hbh***. From 26 mg (0.10 mmol) of TMS-alkynol **4h**, and after chromatography of the residue using hexanes/ethyl acetate (7:3) as eluent, gave compound **3hbh** (25 mg, 41%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 8.14 (m, 2H), 7.90 (m, 2H), 7.70 (m, 2H), 7.59 (m, 2H), 7.30 (m, 1H), 6.92 (m, 1H), 6.82 (m, 2H), 4.41 (q, 2H, J = 7.13 Hz), 3.17 (s, 3H), 1.88 (t, 3H, J = 7.13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 194.6, 166.3, 165.8, 147.0, 145.1, 137.8, 134.1, 132.2 (2C), 131.7, 130.9, 130.4 (2C), 130.3 (2C), 128.9, 128.2 (2C), 127.3, 123.4, 122.2, 120.1, 108.6, 61.4, 26.0, 14.3; IR ($CHCl_3$, cm^{-1}): ν 1714, 1610; HRMS (ES): calcd for $C_{26}H_{21}BrNO_4$ $[M+H]^+$: 490.0648; found: 490.0671.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03006.

Copies of NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Vicente Gotor on the occasion of his 70th birthday.

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Advanced Synthesis & Catalysis

Photopromoted Entry to Benzothiophenes, Benzoselenophenes, 3*H*-Indoles, Isocoumarins, Benzosultams, and (Thio)flavones by Gold-Catalyzed Arylative Heterocyclization of Alkynes

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Abstract: Visible light-promoted and gold-photoredox-catalyzed reactions of heteroatom (N, S, Se, O) tethered alkynes with arenediazonium salts selectively proceeded to build vicinal diaryl-substituted 2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides (benzosultams), benzoselenophenes, benzothiophenes, 4*H*-chromen-4-ones (flavones), 3*H*-indoles, 1*H*-isochromen-1-ones (isocoumarins), and 4*H*-thiochromen-4-ones (thioflavones). Moreover, the utility of functionalized 3*H*-indoles as precursors for further elaboration has been demonstrated with the switchable and facile preparation of 1*H*-indoles, 2-oxindoles, and 3-oxindolines.

Keywords: alkynes; cyclization; gold; heterocyclic compounds; synthetic methods

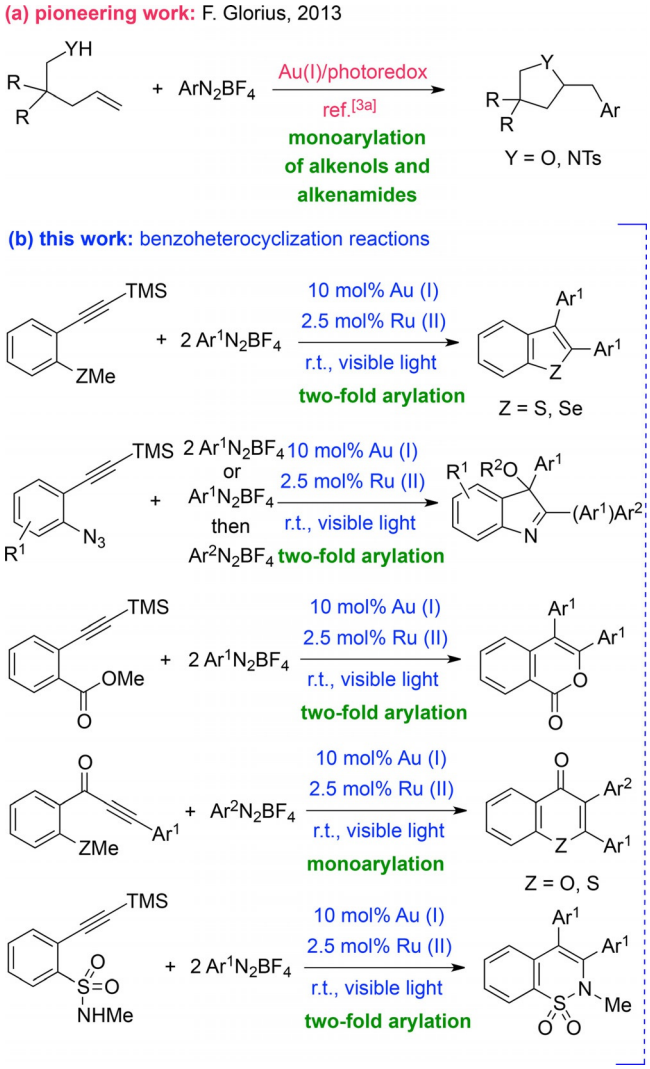
Introduction

Homogeneous gold catalysis has been developed as a potent tool in the field of synthetic organic chemistry. Particularly attractive is the activation of alkenes, alkynes and allenes by cationic gold(I) species.[1] However, Au(I)/Au(III) catalytic cycles cannot be accessed through the traditional gold(I)-catalyzed processes, and super-stoichiometric amounts of a strong oxidant are required for surpassing the high redox potential of Au(I)/Au(III).[2] Taking into account the above limitations, it is not surprising that gold-catalyzed cross-coupling strategies are a less explored field. Glorius and, later, Toste developed a smart strategy for avoiding the drawback of the inclusion of strong oxidants,[3] which takes advantage of a photoredox catalyst and a diazonium salt.[4] Hashmi and Barriault developed gold-only photoredox chemistry through the use of dinuclear complexes of gold as photoredox catalysts.[5]

On the other hand, the widespread presence of heterocycles in both natural products and synthetic drugs, as well as in advanced materials, explains the interest in the preparation of these cyclic frameworks. This area is clearly dominated by palladium catalysis, which usually demands elevated temperatures and the use of ligands and bases. Besides, the incorporation of aryl substituents to the heterocyclic core is performed by the use of aryl halides, which are not always readily available. Aiming to surmount these deficiencies, we were motivated to include diazonium salts and visible light in a comprehensive gold-catalyzed arylative heterocycle formation. Due to environmental concerns, the development of a photocatalyzed arylative synthesis at room temperature may be a great achievement. We wish to describe herein the unique use of diazonium salts as a radical source in the cooperative gold-photoredox-catalyzed synthesis of benzofused heterocycles (Scheme 1).[6]

Results and Discussion

(2-Ethynylphenyl)(methyl)sulfane **1a-H-SMe** and phenyldiazonium salt **2a** were chosen as model substrates to examine their reactivity under cooperative gold and photoredox catalysis.[7] Our aim was the *in situ* generation of a methyl[2-(arylethynyl)phenyl]sul-

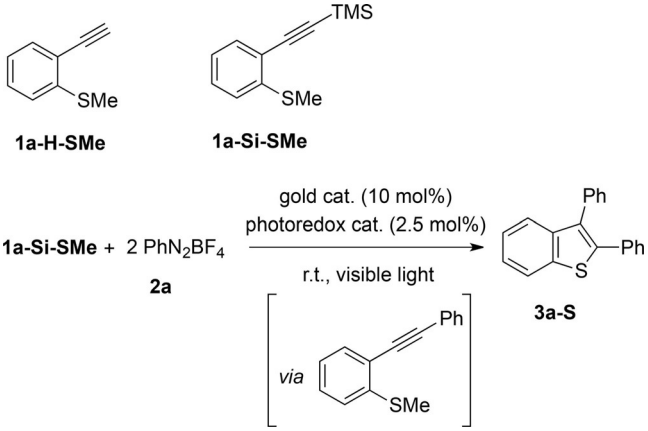


Scheme 1. Dual gold- and photoredox-catalyzed heterocyclization reactions: Previous and current strategies. TMS = trimethylsilyl.

fane from a gold-catalyzed sila-Sonogashira-type coupling, which can be further trapped by the nucleophile sulfur with a concomitant second arylation in a domino sequence. This premise deals with difficulties and presents an initial challenge because the photoredox-gold-catalyzed arylation of sulfur derivatives has not yet been reported. Besides, we need that the starting material undergoes a relatively fast coupling at the alkyne site, in comparison with the heterocyclization event. Substrate **1a-H-SMe** provided benzothiophene **3a-S** in a promising 27% yield. A significant improvement was detected with the use of TMS-capped alkyne **1a-Si-SMe**,[8] which was considered as a viable precursor in the synthesis of 2,3-diarylbenzothiophenes. We initiated our optimization studies using various gold(I) complexes and the ruthenium salt $[Ru(bpy)_3](PF_6)_2$ (bpy = 2,2′-bipyridine) as shown in Table 1. After the evaluation of different conditions, PPh_3AuCl (10 mol%) in combination with $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) provided an impressive yield (94%) of 2,3-diphenylbenzothiophene **3a-S** (entry 3, Table 1). When the loading of PPh_3AuCl was increased from 10 mol% to 20 mol%, it resulted in just a little improvement of the yield (95%) (entry 5, Table 1). Decreasing the amount of PPh_3AuCl from 10 mol% to 5 mol% produced an appreciable reduction of the yield (64%) (entry 6, Table 1). Inferior results were obtained when the reaction was carried out in presence of other photoactive complexes such as $[Ir(ppy)_2(dtbbpy)](PF_6)_2$ (ppy = 2-phenylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) (entry 4, Table 1). Also, alternative gold(I) sources such as [AuClIPr] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] and $[(Ph_3P)AuNTf_2]$ were inefficient (entries 1 and 2, Table 1).

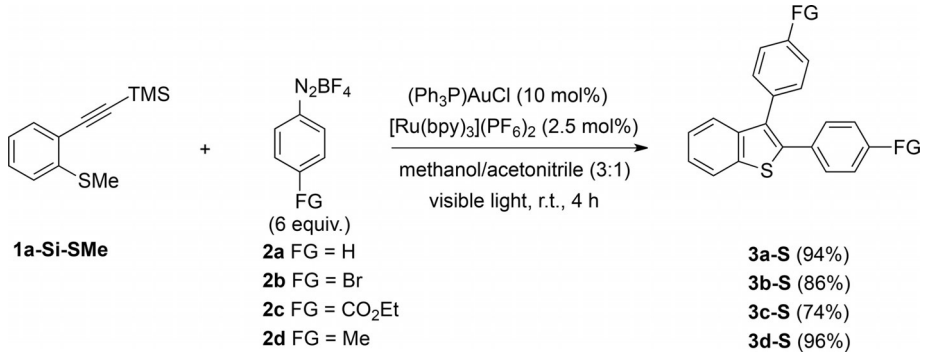
We applied the above reaction conditions to differently functionalized arenediazonium salts **2** (Scheme 2). Substitution was tolerated in the diarylative thiacyclizations of **1a-Si-SMe**, with the presence at the arenediazonium salt of electron-withdrawing

Table 1. Screening of the reaction conditions for benzothiophene formation through light-driven gold/photoredox-co-catalyzed diarylative thiacyclization.[a]



Entry	Gold Catalyst	Photocatalyst[b]	Yield [%][c]
1	[IPrAuCl]	[Ru]	–
2	$[(Ph_3P)AuNTf_2]$	[Ru]	–
3	$[(PPh_3)AuCl]$	[Ru]	94
4	$[(PPh_3)AuCl]$	[Ir]	63
5	$[(PPh_3)AuCl]$[d]	[Ru]	95
6	$[(PPh_3)AuCl]$[e]	[Ru]	64
7	$[(PPh_3)AuCl]$	[Ru]	5[f]

[a] Unless otherwise noted, all reactions were carried out in methanol/acetonitrile (3:1) at room temperature.
[b] [Ru] = $[Ru(bpy)_3](PF_6)_2$, [Ir] = $[Ir(ppy)_2(dtbbpy)](PF_6)_2$.
[c] Yield of pure, isolated product with correct analytical and spectral data.
[d] Catalyst loading of 20 mol%.
[e] Catalyst loading of 5 mol%.
[f] The reaction was carried out in DMF.



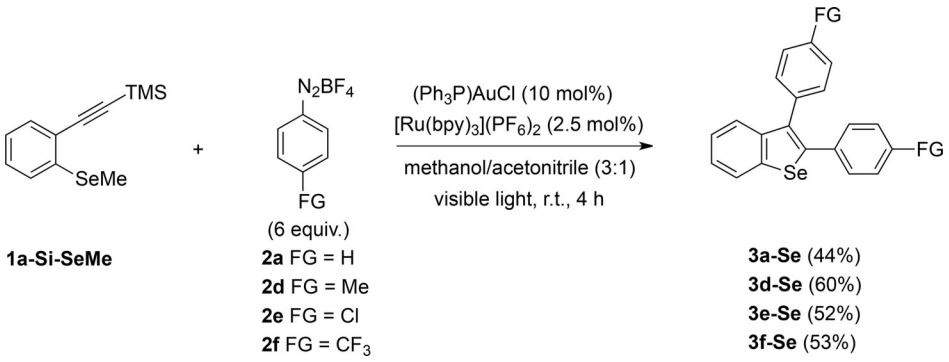
Scheme 2. Cooperative gold-photoredox catalysis for the synthesis of 2,3-diarylbenzothiophenes **3-S**.

groups (CO_2Et, CF_3) as well as halogens (Br) and weakly electron-donating groups (Me). The results depicted in the above scheme show the effectiveness of this methodology for the smooth preparation of a variety of 2,3-diarylbenzothiophenes **3-S**.[9]

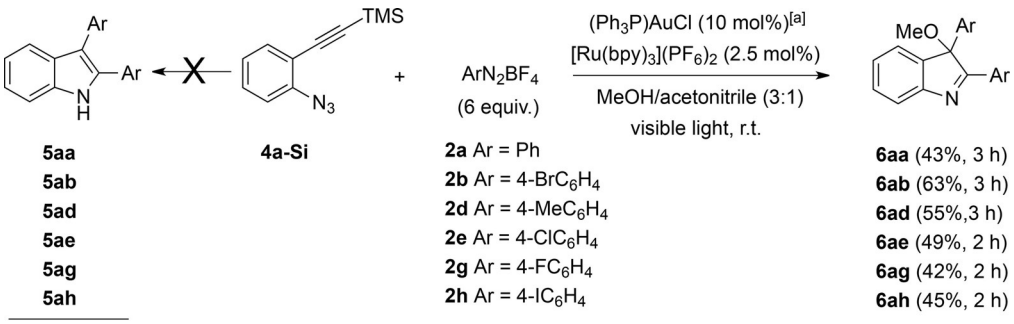
To further probe the scope and versatility of the arylative carbon-chalcogen cyclization reaction, trimethyl[(2-methylselanylphenyl)ethynyl]silane **1a-Si-SeMe** was used to react with phenyldiazonium salt **2a** under the optimized conditions for the formation of 2,3-diaryl benzothiophenes **3-S**. As depicted in Scheme 3, the diarylation/C–Se bond formation sequence proceeded to afford 2,3-diarylbenzoselenophene **3a-Se**, but less efficiently. Precursor **1a-Si-SeMe** reacted well with several arenediazonium salts **2** bearing diverse substitution and gave rise under mild conditions to the desired selenoheterocycles **3-Se**, a type of organic molecule which is prevalent both in drugs and in advanced materials (Scheme 3).

Continuing to explore different functionalities at the TMS-protected alkynes and taking into account that the azide moiety is a versatile nitrogen source,[10] we decided to test azidobenzene-tethered alkynes.[11] The above reaction conditions for TMS-sulfane **1a-Si-SMe** were also applicable for TMS-(ethynyl)azidobenzene **4a-Si**,[12] but it exhibited different reactivity. The lack of formation of expected 2,3-diaryl 1*H*-indoles of type **5** was observed, which should point to a marked directing effect of the heteroatomic nucleophile functionality. In view of the structure of adduct **6a**, the participation of methanol as a nucleophile is apparent. Noteworthy, this interesting reactivity switch allowed the formation of functionalized 3*H*-indoles **6aa–ah** through a diarylative aminocyclization/hydroalkoxylation sequence (Scheme 4). Halogenated or weakly activated arenediazonium salts turned out to be suitable coupling partners. However, diazonium salts having strong electron-withdrawing groups (NO_2 and CF_3) failed to give the desired indole. Instead, alkenes **7** were formed (Scheme 5). Apparently, the electron-poor aryl alkyne intermediate disfavors the aminocyclization with the azide moiety and the competitive intermolecular nucleophilic addition of methanol dominates.

Next, under the optimized reaction conditions, the reactivities of several TMS-(ethynyl)azidobenzenes **4-Si** with arenediazonium salt **2b** were examined (Scheme 6). The power of this methodology was further demonstrated with the use of different alcohols (ethanol, 2-propanol, *tert*-butyl alcohol, and methanol-d_3) instead of methanol to give adducts **6ab-Et**, **6ab-*i*Pr**, **6ab-*t*Bu**, and **6ab-CD_3** (Scheme 6). Besides, several substituents could be incorporated in to the starting materials, which offers the formation of a vari-



Scheme 3. Cooperative gold-photoredox catalysis for the synthesis of 2,3-diarylbenzoselenophenes **3-Se**.



5aa **5ab** **5ad** **5ae** **5ag** **5ah**

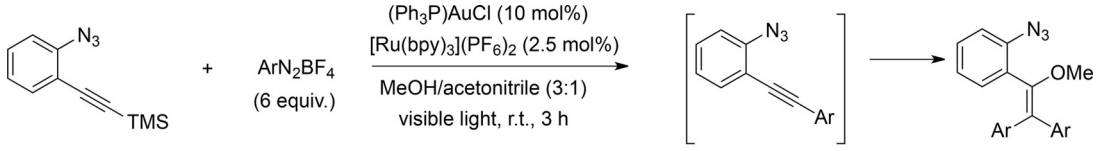
4a-Si

2a Ar = Ph
2b Ar = 4-BrC_6H_4
2d Ar = 4-MeC_6H_4
2e Ar = 4-ClC_6H_4
2g Ar = 4-FC_6H_4
2h Ar = 4-IC_6H_4

6aa (43%, 3 h)
6ab (63%, 3 h)
6ad (55%,3 h)
6ae (49%, 2 h)
6ag (42%, 2 h)
6ah (45%, 2 h)

[a] For a full conversion, the complex was added in two separate portions with a 30 min time interval.

Scheme 4. Cooperative gold-photoredox catalysis for the synthesis of 2,3-diaryl-3*H*-indoles **6**.



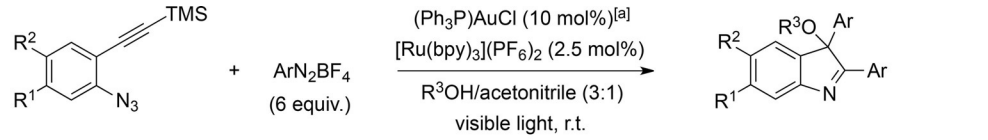
4a-Si

2f Ar = 4-$CF_3C_6H_4$
2i Ar = 4-$NO_2C_6H_4$

4af-Ar
4ai-Ar

7af (38%)
7ai (55%)

Scheme 5. Cooperative gold-photoredox catalysis for the diarylative hydroalkoxylation of (ethynyl)azidobenzene **4a-Si** with strongly deactivated arenediazonium salts.



4a-Si R^1 = H, R^2 = H
4a-Si R^1 = H, R^2 = H
4a-Si R^1 = H, R^2 = H
4a-Si R^1 = H, R^2 = H
4b-Si R^1 = Cl, R^2 = H
4c-Si R^1 = F, R^2 = H
4d-Si R^1 = H, R^2 = Me
4e-Si R^1 = H, R^2 = CO_2Et
4f-Si R^1 = H, R^2 = Cl

2b

Ar = 4-BrC_6H_4

6ab-Et R^3 = Et (57%, 3 h)
6ab-*i*Pr R^3 = *i*-Pr (55%, 5 h)
6ab-*t*Bu R^3 = *t*-Bu (23%, 12 h)
6ab-CD_3 R^3 = CD_3 (59%, 2 h)
6bb R^3 = Me (49%, 2 h)
6cb R^3 = Me (52%, 2 h)
6db R^3 = Me (41%, 3 h)
6eb R^3 = Me (44%, 3 h)
6fb R^3 = Me (46%, 2 h)

[a] For a full conversion, the complex was added in two separate portions with a 30 min time interval.

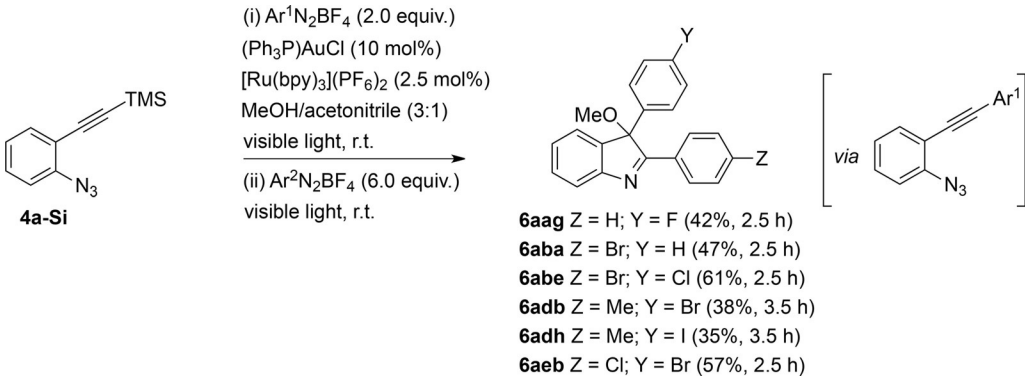
Scheme 6. Cooperative gold-photoredox catalysis for the synthesis of differently substituted 2,3-diaryl-3*H*-indoles **6**.

ety of functionalized 3*H*-indoles. The reaction yields (^{1}H NMR) were excellent before purification because no side-products were detected when the starting material was fully converted. However, partial decomposition was observed on sensitive 3*H*-indoles **6** during chromatographic purification.

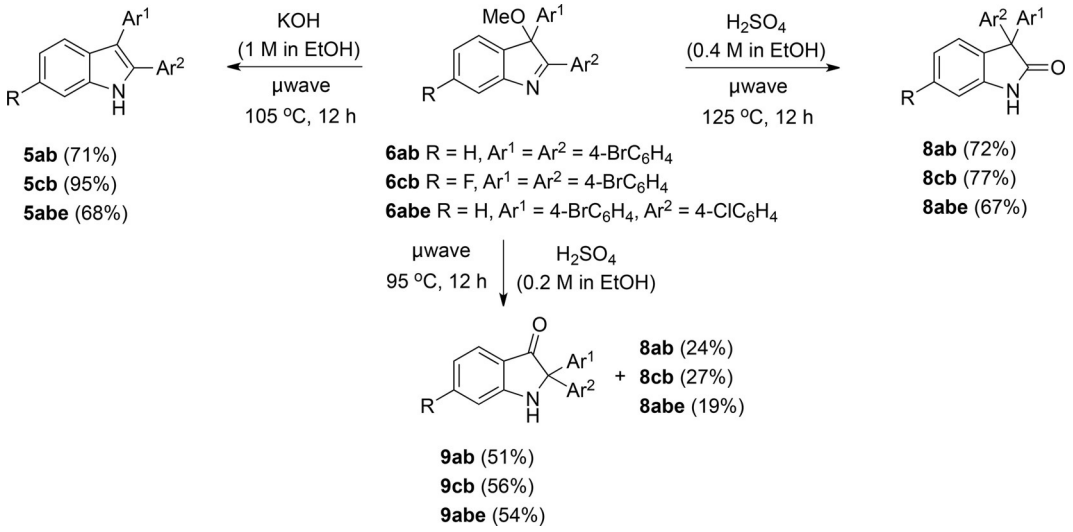
To fully exploit the potential of this methodology, we reacted [(2-azidophenyl)ethynyl]trimethylsilane **4a-Si** with a pair of different diazonium salts **2**. Initial Hiyama coupling of TMS-precursor **4a-Si** with the first diazonium salt **2** provided 1-azido-2-(arylethynyl)benzene intermediates. Without the need of isolation, these intermediates afforded the final differently diarylated 3*H*-indoles **6** after a second coupling with another diazonium salt (Scheme 7). Thus, TMS-(ethynyl)azidobenzene **4a-Si** acts as a versatile building block for the double crossed diarylation reaction, and allows for the preparation of crossover adducts in a convenient and modular way.

Besides, the utility of 3-alkoxy-2,3-diaryl-3*H*-indoles **6** as precursors for further elaboration has been demonstrated with the controlled preparation of *N*-unprotected indoles **5**, 2-oxindoles **8** and 3-oxindolines **9** through base- or acid-promoted rearrangement reactions (Scheme 8).[13] Possibly, the driving force of these reorganizations may be related to the gain in stability associated with the formation of 1*H*-indole, indolinone and indolone systems.

With thia-, selena-, and azido-(TMS-ethynyl)benzenes **1a-Si-SMe**, **1a-Si-SeMe**, and **4-Si** found to be

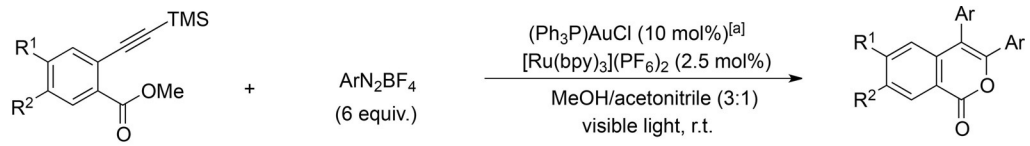


Scheme 7. Cooperative gold-photoredox catalysis for the crossed preparation of 2,3-diaryl-3*H*-indoles **6**.



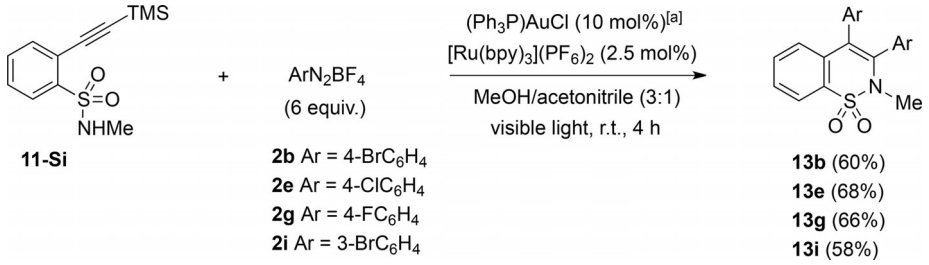
Scheme 8. Synthetic transformations of 3-methoxy-2,3-diaryl-3*H*-indoles **6**.

compatible with the diarylative five-membered heterocyclization reaction, structurally different precursors were investigated to further expand the scope of the reaction to six-membered benzo-fused heterocycles. For the investigation of the scope of the sequence, some potential precursors, esters **10-Si** and sulfonamide **11-Si**, were prepared. Interestingly, isocoumarins **12** were obtained in fair yields by the light-driven gold/photoredox-co-catalyzed double arylation/oxycyclization of 2-[(trimethylsilyl)ethynyl]benzoates **10-Si** (Scheme 9). Notably, regioisomeric five-membered heterocycles were not detected, highlighting the ex-



[a] For a full conversion, the complex was added in two separate portions with a 30 min time interval.

Scheme 9. Cooperative gold-photoredox catalysis for the synthesis of 3,4-diarylisocoumarins **12**.

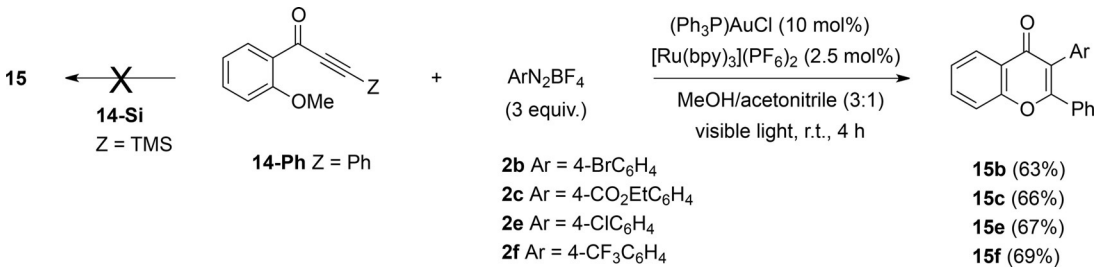


Scheme 10. Cooperative gold-photoredox catalysis for the synthesis of 3,4-diarylbenzosultams **13**.

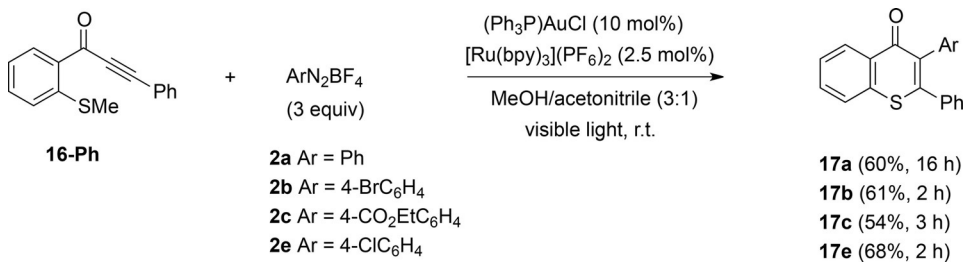
quisite selectivity of the sequence. Starting from 2-[(trimethylsilyl)ethynyl]benzenesulfonamide **11-Si**, the same diarylative protocol afforded benzosultams **13** with satisfactory yields (Scheme 10). It is apparent that in esters **10-Si** and sulfonamide **11-Si** the 6-*endo* oxy- and aza-cyclization pathways are favoured because competitive 5-*exo* heterocyclizations are not involved.

Having in hand (trimethylsilyl)prop-2-yn-1-one **14-Si**, we attempted the double arylation with arenediazonium salt **2a** under the above reaction conditions. However, no reaction was observed (Scheme 11), which shows that the contiguous ketone group in the (trimethylsilyl)ethyne moiety is critical for the suppression of any Hiyama–Sonogashira reaction. Efforts to modify either the gold catalyst or the diazonium salt led to no improvement in reactivity. We decided to implement our planned synthesis of benzo-fused heterocycles by replacing the TMS group with an aryl substituent. Convincing confirmation for the negative effect of the alkynone framework on the sila-coupling but not on the heterocyclization event, was definitively obtained by the fruitful accomplishment of the monoarylative/heterocyclization in aryl-terminated alkynone **14-Ph** whereby the synthesis of 4*H*-chromen-4-ones **15** has been attained (Scheme 11). The successful cyclization of the heteroatom-linked alkynone core was further confirmed by the light-driven gold/photoredox-co-catalyzed arylative thiacyclization reaction of the sulfa-derivative **16-Ph** with several diazonium salts **2** to afford 4*H*-thiochromen-4-ones **17** (Scheme 12). The detected regiochemistry of both ring closures (6-*endo* oxy- and thia-cyclizations) is in agreement with the results of Scheme 9 and Scheme 10.

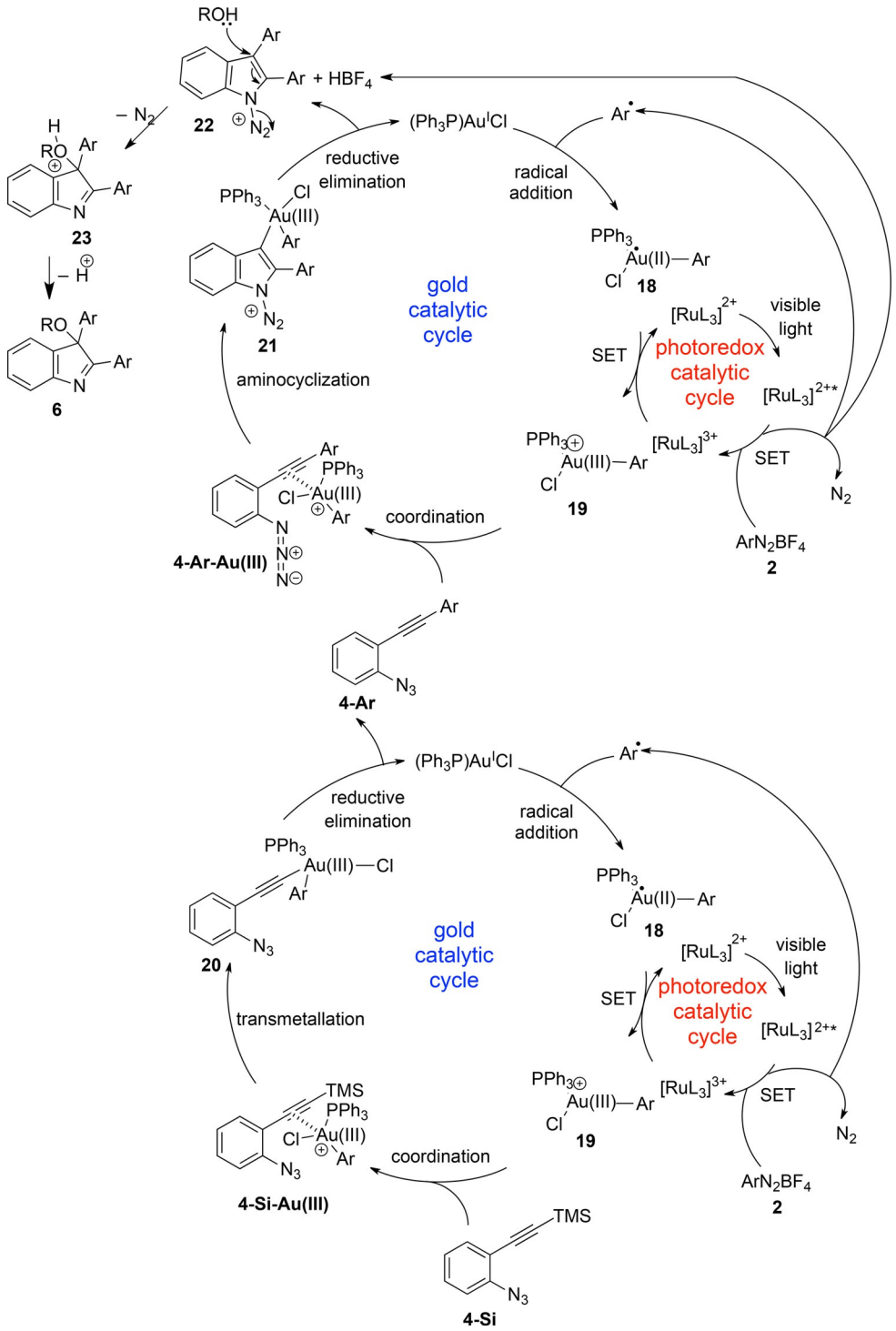
Although Hashmi[14] and Shi[15] have independently shown that no photoredox catalysts are required for related reactions, a control experiment verified that our reactions operate through $[Ru(bpy)_3](PF_6)_2$ photoredox. Indeed, starting either from **1a-Si-SMe** or **4a-Si** no reaction occurred in the absence of the photosensitizer. The critical role of light in the domino reaction was probed with the precursors **1a-Si-SMe** or **4a-Si** being recovered when the reactions were run



Scheme 11. Cooperative gold-photoredox catalysis for the synthesis of 3-arylflavones **15**.



Scheme 12. Cooperative gold-photoredox catalysis for the synthesis of 3-arylthioflavones **17**.



Scheme 13. Rationalization for the gold-photoredox cocatalyzed preparation of 3-alkoxy-2,3-diaryl-3*H*-indoles **6** from TMS-(ethynyl)azidobenzenes **4-Si** and diazonium salts **2**.

with all the reagents but without irradiation. A tentative mechanistic proposal for the generation of 3-alkoxy-2,3-diaryl-3*H*-indoles **6** from 2-[(trimethylsilyl)ethynyl]azidobenzenes **4-Si**, diazonium salts **2** and light under dual gold-photoredox cocatalysis is summarized in Scheme 13. Initially, irradiation of the Ru(II)-based photoredox catalyst results in the formation of an aryl radical from diazonium salts **2** after extrusion of dinitrogen (bottom catalytic cycle, right side). This key reactive species is able to be coupled with the gold(I) precatalyst to allow the formation of unstable organogold(II) intermediate **18**, which rapidly evolves to the cationic organogold(III) derivative **19**, a strong electrophile, through the oxidative action

of Ru(III) and concomitant liberation of [Ru(bpy)$_3$](PF$_6$)$_2$ into the catalytic cycle. Next, TMS-(ethynyl)azidobenzenes **4-Si** enter the gold catalytic sequence (bottom catalytic cycle, left side), forming complexes **4-Si**-Au(III) through alkyne coordination with the gold complex. Either the transmetallation of the C(*sp*)–Si bond or the nucleophilic attack from the azide group can be effectively produced. Apparently, the silicon/gold interchange is preferred to the aminoauration. Then, Si–Au transmetallation should produce gold acetylide species **20**, which suffers reductive elimination paired to aryl transfer and releases 2-(arylethynyl)azidobenzenes **4-Ar** and the gold(I) salt, closing the first gold catalytic cycle (bottom catalytic cycle). The formation of 3-alkoxy-2,3-diaryl-3*H*-indoles **6** from 2-(arylethynyl)azidobenzenes **4-Ar** requires the participation of the organogold(III) species **19** in the azacyclization event. According to the aforementioned comments, a second molecule of arenediazonium salt **2** affords the corresponding aryl radical helped by light and the photoredox catalyst (top catalytic cycle, right side). The N atom attack to the terminal carbon of the triple bond with respect to the azide moiety is facilitated in intermediate **4-Ar-Au(III)** by the coordination of arylgold(III) species **19** with the alkyne functionality of **4-Ar**. After the 5-*endo*-dig azacyclization, the aryl transfer from the Au atom to the C-3 indole carbon leads to intermediate 1*H*-indoles **22**. In concert, the gold(I) precatalyst is regenerated in this pathway (top catalytic cycle, left side). The formation of 3-alkoxy-2,3-diaryl-3*H*-indoles **6** requires the further attack of the alcohol with concomitant nitrogen release.

Conclusions

In conclusion, visible light-promoted and gold-photoredox-catalyzed reactions of heteroatom(N, S, Se, O)-tethered alkyne derivatives with diazonium salts are totally selective to build in a controlled manner vicinal diaryl-substituted 2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides (benzosultams), benzoselenophenes, benzothiophenes, 4*H*-chromen-4-ones (flavones), 3*H*-indoles, 1*H*-isochromen-1-ones (isocoumarins), and 4*H*-thiochromen-4-ones (thioflavones). Besides, the usefulness of 3*H*-indoles has been probed with the facile and divergent synthesis of 1*H*-indoles, 2-oxindoles and 3-oxindolines.

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, or a Bruker Avance-300 spectrometer. NMR spectra were recorded in $CDCl_3$ solution, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm). Low and high resolution mass spectra were taken on an Agilent 6520 Accurate Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

General Procedure for the Photopromoted Gold-Catalyzed Two-Fold Arylation Reaction of Hetero-Subtituted TMS-(Ethynyl)benzenes 1a-Si-SMe, 1a-Si-SeMe, 4a–f-Si, 10a–c-Si, or 11-Si with Diazonium Salts 2; Preparation of 2,3-Diarylbenzothiophenes 3-S, 2,3-Diarylbenzoselenophenes 3-Se, 3-Alkoxy-2,3-diaryl-3*H*-indoles 6, 3,4-Diarylisocoumarins 11, and 3,4-Diarylbenzosultams 13

In a Schlenk tube in the absence of light at −78 °C under an argon atmosphere, Ph_3PAuCl (10 mol%) and [Ru(bpy)$_3$](PF$_6$)$_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arenediazonium salt **2** (6.0 equiv.) in a mixture of MeOH/MeCN (3:1, 5.0 mL). Then, a solution of the appropriate 2-[(trimethylsilyl)ethynyl]benzene **1a-Si-SMe**, **1a-Si-SeMe**, **4a–f-Si**, **10a–c-Si**, or **11-Si** (1.0 mmol) in MeOH/MeCN (3:1, 2.5 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 5 min. For a full conversion in the case of azides **4**, at the beginning the gold salt was added in two separate portions with a 30 min time interval. The reaction mixture was then warmed to room temperature and stirred under irradiation from visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. The addition of Et_3N (2%) to the eluent was neccesary for the purification of acid sensitive 3*H*-indoles **6**. Spectroscopic and analytical data for pure forms of compounds **1a-Si-SMe**, **1a-Si-SeMe**, **4a–f-Si**, **10a–c-Si**, and **11-Si** are give in the following paragraphs.[16]

2,3-Diarylbenzothiophene (3a-S): From 22 mg (0.10 mmol) of TMS-alkyne **1a-Si-SMe**, and after chromatography of the residue using hexanes as eluent, gave compound **3a-S** as a colourless solid; yield: 27 mg (94%); mp 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.85–7.79 (m, 1H, CH^{Ar}), 7.54–7.50 (m, 1H, CH^{Ar}), 7.31–7.15 (m, 12H, 12CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 141.2 ($C^{Ar\text{-}q}$), 139.9 ($C^{Ar\text{-}q}$), 139.2 ($C^{Ar\text{-}q}$), 135.8 ($C^{Ar\text{-}q}$), 134.6 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 130.8 (2CH^{Ar}), 130.0 (2CH^{Ar}), 129.0 (2CH^{Ar}), 128.7 (2CH^{Ar}), 128.1 (CH^{Ar}), 127.7 (CH^{Ar}), 124.9 (CH^{Ar}), 124.8 (CH^{Ar}), 123.7 (CH^{Ar}), 122.4 (CH^{Ar}); IR ($CHCl_3$): ν = 1599, 1436 cm^{-1}; HR-MS (ES): *m/z* = 287.0898, calcd. for $C_{20}H_{15}S$ [*M* + H]$^+$: 287.0889.

2,3-Diarylbenzothiophene (3b-S): From 35 mg (0.16 mmol) of TMS-alkyne **1a-Si-SMe**, and after chromatography of the residue using hexanes as eluent, gave compound **3b-S** as a colourless solid; yield: 60 mg (86%); mp 175–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.89 (m,

1H, CH^{Ar}), 7.56 (m, 3H, $3CH^{Ar}$), 7.40 (m, 4H, $4CH^{Ar}$), 7.19 (m, 4H, $4CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 140.3 ($C^{Ar\text{-}q}$), 138.8 ($C^{Ar\text{-}q}$), 138.6 ($C^{Ar\text{-}q}$), 134.1 ($C^{Ar\text{-}q}$), 132.9 ($C^{Ar\text{-}q}$), 132.3 ($C^{Ar\text{-}q}$), 132.1 ($2CH^{Ar}$), 132.0 ($2CH^{Ar}$), 131.7 ($2CH^{Ar}$), 131.1 ($2CH^{Ar}$), 124.9 (CH^{Ar}), 124.8 (CH^{Ar}), 123.1 (CH^{Ar}), 122.3 ($C^{Ar\text{-}q}$), 122.2 (CH^{Ar}), 121.8 ($C^{Ar\text{-}q}$); IR ($CHCl_3$): ν = 1533, 1484 cm^{-1}; HR-MS (ES): m/z = 442.9087, calcd. for $C_{20}H_{13}Br_2S$ $[M+H]^+$: 442.9099.

2,3-Diarylbenzoselenophene (3d-Se): From 26 mg (0.10 mmol) of TMS-alkyne **1a-Si-SeMe**, and after chromatography of the residue using hexanes as eluent, gave compound **3d-Se** as a colourless solid; yield: 28 mg (60%); mp 140–142 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.08–8.04 (m, 1H, CH^{Ar}), 7.67–7.63 (m, 1H, CH^{Ar}), 7.47–7.30 (m, 8H, $8CH^{Ar}$), 7.21–7.17 (m, 2H, $2CH^{Ar}$), 2.56 (s, CH_3), 2.46 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 143.8 ($C^{Ar\text{-}q}$), 143.2 ($C^{Ar\text{-}q}$), 140.2 ($C^{Ar\text{-}q}$), 137.4 ($C^{Ar\text{-}q}$), 136.9 ($C^{Ar\text{-}q}$), 135.9 ($C^{Ar\text{-}q}$), 133.8 ($C^{Ar\text{-}q}$), 133.4 ($C^{Ar\text{-}q}$), 130.4 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 129.4 ($2CH^{Ar}$), 129.1 ($2CH^{Ar}$), 125.6 (CH^{Ar}), 125.2 (CH^{Ar}), 124.6 ($2CH^{Ar}$); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 528.9 (s, 1Se); IR ($CHCl_3$): ν = 1506, 1439, 810 cm^{-1}; HR-MS (ES): m/z = 363.0632, calcd. for $C_{22}H_{19}Se$ $[M+H]^+$: 363.0647.

2,3-Diarylbenzoselenophene (3e-Se): From 26 mg (0.10 mmol) of TMS-alkyne **1a-Si-SeMe**, and after chromatography of the residue using hexanes as eluent, gave compound **3e-Se** as a colourless solid; yield: 21 mg (52%); mp 198–200 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.97–7.94 (m, 1H, CH^{Ar}), 7.52–7.49 (m, 1H, CH^{Ar}), 7.42–7.27 (m, 4H, $4CH^{Ar}$), 7.26–7.17 (m, 6H, $6CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 143.0 ($C^{Ar\text{-}q}$), 142.3 ($C^{Ar\text{-}q}$), 140.5 ($C^{Ar\text{-}q}$), 135.6 ($C^{Ar\text{-}q}$), 134.9 ($C^{Ar\text{-}q}$), 134.4 ($C^{Ar\text{-}q}$), 133.8 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 131.9 ($2CH^{Ar}$), 131.0 ($2CH^{Ar}$), 129.1 ($2CH^{Ar}$), 128.7 ($2CH^{Ar}$), 125.5 (CH^{Ar}), 125.4 (CH^{Ar}), 125.2 (CH^{Ar}), 125.0 (CH^{Ar}); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 538.9 (s, 1Se); IR ($CHCl_3$): ν = 1484, 1089, 833 cm^{-1}; HR-MS (ES): m/z = 402.9570 calcd. for $C_{20}H_{13}Cl_2Se$ $[M+H]^+$: 402.9554.

3-Alkoxy-2,3-diaryl-3*H*-indole (6ab): From 30 mg (0.14 mmol) of TMS-azide **4a-Si**, and after chromatography of the residue using hexanes/Et_2O (97:3) containing NEt_3 (2%) as eluent, gave compound **6ab** as a yellow oil; yield: 40 mg (63%); ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.97 (m, 2H, $2CH^{Ar}$), 7.68 (d, 1H, J = 7.7 Hz, CH^{Ar}), 7.51 (m, 2H, $2CH^{Ar}$), 7.41 (m, 1H, CH^{Ar}), 7.37 (m, 2H, $2CH^{Ar}$), 7.22 (d, 1H, J = 6.6 Hz, CH^{Ar}), 7.19 (m, 2H, $2CH^{Ar}$), 7.11 (d, 1H, J = 6.9 Hz, CH^{Ar}), 3.06 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 177.2 (N=C), 153.2 ($C^{Ar\text{-}q}$), 139.7 ($C^{Ar\text{-}q}$), 138.3 ($C^{Ar\text{-}q}$), 131.9 ($2CH^{Ar}$), 130.2 (CH^{Ar}), 130.0 ($C^{Ar\text{-}q}$), 129.9 ($2CH^{Ar}$), 127.2 (CH^{Ar}), 126.4 ($C^{Ar\text{-}q}$), 126.2 ($2CH^{Ar}$), 123.4 (CH^{Ar}), 121.7 ($C^{Ar\text{-}q}$), 121.6 (CH^{Ar}), 92.9 (OC^q), 52.6 (OCH_3); IR ($CHCl_3$): ν = 1728 (N=C), 1079 cm^{-1} (C–O); HR-MS (ES): m/z = 455.9601, calcd. for $C_{21}H_{16}Br_2NO$ $[M+H]^+$: 455.9593.

3-Alkoxy-2,3-diaryl-3*H*-indole (6ab-CD_3): The reaction was run in CD_3OD instead MeOH. From 30 mg (0.14 mmol) of azide **4a-Si**, and after chromatography of the residue using hexanes/Et_2O (97:3) as eluent containing NEt_3 (2%), gave compound **6ab-CD_3** as a yellow oil; yield: 38 mg (59%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.87 (m, 2H, $2CH^{Ar}$), 7.58 (d, 1H, J = 7.7 Hz, CH^{Ar}), 7.41 (m, 2H, $2CH^{Ar}$), 7.29 (m, 3H, $3CH^{Ar}$), 7.10 (m, 2H, $2CH^{Ar}$), 7.01 (d, 1H, J = 6.8 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 177.2 (N=C), 153.3 ($C^{Ar\text{-}q}$), 139.7 ($C^{Ar\text{-}q}$), 138.3 ($C^{Ar\text{-}q}$), 131.9 ($2CH^{Ar}$), 130.2 (CH^{Ar}), 130.1 ($C^{Ar\text{-}q}$), 129.9 ($2CH^{Ar}$), 127.2 (CH^{Ar}), 126.4 ($C^{Ar\text{-}q}$), 126.2 ($2CH^{Ar}$), 123.4 (CH^{Ar}), 121.7 ($C^{Ar\text{-}q}$), 121.6 (CH^{Ar}), 92.9 (OC^q); D (^2H) NMR (107 MHz, $CDCl_3$, 25 °C): δ = 3.04; IR ($CHCl_3$,): ν = 1723 (N=C), 1076 cm^{-1} (C–O); HR-MS (ES): m/z = 458.9784, calcd. for $C_{21}H_{13}D_3Br_2NO$ $[M+H]^+$: 458.9782.

3,4-Diarylisocoumarin (12ad): From 40 mg (0.18 mmol) of TMS-alkyne **10a-Si**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **12ad** as a colourless solid; yield: (41 mg (70%); mp 165–167 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.39 (d, 1H, J = 7.8 Hz, CH^{Ar}), 7.62 (m, 1H, CH^{Ar}), 7.50 (t, 1H, CH^{Ar}), 7.19 (m, 7H, $7CH^{Ar}$), 7.01 (m, 2H, $2CH^{Ar}$), 2.43 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.4 (C=O), 150.9 (C=C), 139.2 ($C^{Ar\text{-}q}$), 139.0 ($C^{Ar\text{-}q}$), 137.8 ($C^{Ar\text{-}q}$), 134.5 (CH^{Ar}), 131.4 ($C^{Ar\text{-}q}$), 131.0 ($2CH^{Ar}$), 130.1 ($C^{Ar\text{-}q}$), 129.8 ($2CH^{Ar}$), 129.4 (CH^{Ar}), 129.0 ($2CH^{Ar}$), 128.6 ($2CH^{Ar}$), 127.8 (CH^{Ar}), 125.3 (CH^{Ar}), 120.3 ($C^{Ar\text{-}q}$), 116.3 (C=C), 21.3 (CH_3), 21.2 (CH_3); IR ($CHCl_3$): ν = 1715 cm^{-1} (C=O); HR-MS (ES): m/z = 327.1388, calcd. for $C_{23}H_{19}O_2$ $[M+H]^+$: 327.1380.

3,4-Diarylisocoumarin (12af): From 35 mg (0.15 mmol) of TMS-alkyne **10a-Si**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **12af** as a colourless solid; yield: 44 mg (68%); mp 155–157 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.45 (dd, 1H, J = 7.9, 1.3 Hz, CH^{Ar}), 7.71 (m, 3H, $3CH^{Ar}$), 7.60 (m, 1H, CH^{Ar}), 7.50 (m, 2H, $2CH^{Ar}$), 7.43 (m, 4H, $4CH^{Ar}$), 7.13 (d, 1H, J = 7.8 Hz, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.4 (C=O), 149.7 (C=C), 137.7 (d, $J_{C,F}$ = 1.3 Hz, $C^{Ar\text{-}q}$), 137.6 ($C^{Ar\text{-}q}$), 135.9 (d, $J_{C,F}$ = 1.0 Hz, $C^{Ar\text{-}q}$), 135.0 (CH^{Ar}), 131.7 ($2CH^{Ar}$), 131.0 (q, $J_{C,F}$ = 32.7 Hz, $C^{Ar\text{-}q}$–CF_3), 130.8 (q, $J_{C,F}$ = 32.8 Hz, $C^{Ar\text{-}q}$–CF_3), 129.9 (CH^{Ar}), 129.5 ($2CH^{Ar}$), 129.0 (CH^{Ar}), 126.3 (q, $J_{C,F}$ = 3.7 Hz, $2CH^{Ar}$), 125.2 (CH^{Ar}), 125.1 (q, J = 3.8 Hz, $2CH^{Ar}$), 123.8 (q, $J_{C,F}$ = 272.4 Hz, CF_3), 123.6 (q, $J_{C,F}$ = 272.4 Hz, CF_3), 120.5 ($C^{Ar\text{-}q}$), 116.90 (C=C), 103.4 (CH^{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −62.9 (s, 3F, CF_3), −63.2 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1735 cm^{-1} (C=O); HR-MS (ES): m/z = 435.0814, calcd. for $C_{23}H_{13}F_6O_2$ $[M+H]^+$: 435.0814.

3,4-Diarylisocoumarin (12bb): From 41 mg (0.11 mmo0l) of TMS-alkyne **10b-Si**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **12bb** as a colourless solid; yield: 37 mg (72%); mp 142–144 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (dd, 1H, J = 8.3, 2.8 Hz, CH^{Ar}), 7.60 (m, 2H, $2CH^{Ar}$), 7.39 (m, 3H, $3CH^{Ar}$), 7.16 (m, 5H, $5CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.0 (d, $J_{C,F}$ = 251.5 Hz, $C^{Ar\text{-}q}$–F), 163.7 (d, $J_{C,F}$ = 3.5 Hz, C=O), 149.5 (d, $J_{C,F}$ = 2.6 Hz, C=C), 134.7 (d, $J_{C,F}$ = 2.7 Hz, $C^{Ar\text{-}q}$), 132.7 ($2CH^{Ar}$), 132.6 ($2CH^{Ar}$), 131.4 ($2CH^{Ar}$), 131.2 ($C^{Ar\text{-}q}$), 130.6 ($2CH^{Ar}$), 127.7 (d, $J_{C,F}$ = 7.8 Hz, CH^{Ar}), 123.8 ($C^{Ar\text{-}q}$), 123.3 ($C^{Ar\text{-}q}$), 123.1 (d, $J_{C,F}$ = 22.8 Hz, CH^{Ar}), 122.9 ($C^{Ar\text{-}q}$), 122.2 (d, $J_{C,F}$ = 8.2 Hz, $C^{Ar\text{-}q}$), 115.5 (d, $J_{C,F}$ = 0.9 Hz, C=C), 115.3 (d, $J_{C,F}$ = 23.3 Hz, CH^{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −110.31 (s, 1F, C-F); IR ($CHCl_3$): ν = 1737 cm^{-1} (C=O); HR-MS (ES): m/z = 472.9192, calcd. for $C_{21}H_{11}Br_2FO_2$ $[M+H]^+$: 472.9183.

3,4-Diarylbenzosultam (13e): From 26 mg (0.10 mmol) of TMS-alkyne **11-Si**, and after chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent, gave compound **13e** as a colourless oil; yield: 28 mg (68%). ^1H NMR

(300 MHz, $CDCl_3$, 25 °C): δ = 8.00–7.96 (m, 1H, CH^{Ar}), 7.55–7.53 (m, 2H, 2CH^{Ar}), 7.30–7.28 (m, 3H, 3CH^{Ar}), 7.24–7.22 (m, 4H, 2CH^{Ar}), 7.15 (d, 2H, J = 7.9 Hz, 2CH^{Ar}), 2.99 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 140.0 ($C^{Ar\text{-}q}$), 134.9 ($C^{Ar\text{-}q}$), 134.1 ($C^{Ar\text{-}q}$), 133.6 ($C^{Ar\text{-}q}$), 133.4 ($C^{Ar\text{-}q}$), 132.5 (2CH^{Ar}), 132.3 ($C^{Ar\text{-}q}$), 131.8 (CH^{Ar}), 131.6 ($C^{Ar\text{-}q}$), 131.3 (2CH^{Ar}), 128.6 (2CH^{Ar}), 128.5 (2CH^{Ar}), 128.2 (CH^{Ar}), 127.0 (CH^{Ar}), 123.4 ($C^{Ar\text{-}q}$), 122.0 (CH^{Ar}), 34.5 (CH_3); IR ($CHCl_3$,): ν = 1588 (C=C), 1485, 1337 cm^{-1} (O=S=O); HR-MS (ES): m/z = 416.0277, calcd. for $C_{21}H_{16}Cl_2NO_2S$ $[M+H]^+$: 416.0273.

3,4-Diarylbenzosultam (13g): From 26 mg (0.10 mmol) of TMS-alkyne **11-Si**, and after chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent, gave compound **13g** as a colourless oil; yield: 25 mg (66%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.92–7.89 (m, 1H, CH^{Ar}), 7.48–7.46 (m, 2H, 2CH^{Ar}), 7.31–7.25 (m, 3H, 3CH^{Ar}), 7.20–7.05 (m, 2H, 2CH^{Ar}), 7.02–6.91 (m, 4H, 4CH^{Ar}), 2.94 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.5 (d, 1H, $J_{C,F}$ = 250.0 Hz, $C^{Ar\text{-}q}$–F), 162.0 (d, 1H, $J_{C,F}$ = 250.0 Hz, $C^{Ar\text{-}q}$–F), 140.3 ($C^{Ar\text{-}q}$), 133.7 ($C^{Ar\text{-}q}$), 132.9 162.0 (d, 2H, $J_{C,F}$ = 8.3 Hz, 2CH^{Ar}), 131.9 (d, 2H, $J_{C,F}$ = 8.3 Hz, 2CH^{Ar}), 131.8 (CH^{Ar}), 131.6 ($C^{Ar\text{-}q}$), 131.5 ($C^{Ar\text{-}q}$), 130.0 ($C^{Ar\text{-}q}$), 128.0 (CH^{Ar}), 127.0 (CH^{Ar}), 123.4 ($C^{Ar\text{-}q}$), 121.9 (CH^{Ar}), 115.2 (d, 4H, $J_{C,F}$ = 22.3 Hz, 4CH^{Ar}), 34.4 (s, CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −111.4 (s, 1F, C–F), −114.3 (s, 1F, C–F); IR ($CHCl_3$): ν = 1585 (C=C), 1487, 1335 cm^{-1} (O=S=O); HR-MS (ES): m/z = 384.0860, calcd. for $C_{21}H_{16}F_2NO_2S$ $[M+H]^+$: 384.0864.

General Procedure for the Photopromoted Gold-Catalyzed Cross Double Arylation Reaction of TMS-(ethynyl)azidobenzene 4a-Si with Diazonium Salts 2; Preparation of Crossed 3-methoxy-2,3-diaryl-3*H*-indoles 6aag–6aeb

In a Schlenk tube in the absence of light at −78 °C under an argon atmosphere, Ph_3PAuCl (5 mol%) and $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the first arenediazonium salt **2** (1.5 equiv.) in a mixture of MeOH/MeCN (3:1, 4.0 mL). Then, a solution of the 2-[(trimethylsilyl)ethynyl]azidobenzene **4a-Si** (1.0 mmol) in MeOH/MeCN (3:1, 1.5 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from a visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC, 20–30 min), Ph_3PAuCl (5 mol%) and a solution of the second arenediazonium salt **2** (6.0 equiv.) in a mixture of MeOH/MeCN (3:1, 2.5 mL) were sequentially added. The resulting reaction mixture was stirred at room temperature under irradiation from a visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. The addition of Et_3N (2%) to the eluent was neccesary for the purification of acid-sensitive 3*H*-indoles **6**. Spectroscopic and analytical data for pure forms of crossed adducts **6** are given in the following paragraphs.

3-Methoxy-2,3-diaryl-3*H*-indole (6abe): From 30 mg (0.14 mmol) of TMS-azide **4a-Si**, and after chromatography of the residue using hexanes/Et_2O (97:3) containing NEt_3 (2%) as eluent, gave compound **6abe** as a yellow oil; yield: 35 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.99 (m, 2H, 2CH^{Ar}), 7.59 (d, 1H, J = 7.7 Hz, CH^{Ar}), 7.42 (m, 2H, 2CH^{Ar}), 7.32 (td, 1H, J = 7.6, 1.3 Hz, CH^{Ar}), 7.15 (m, 5H, 5CH^{Ar}), 7.02 (d, 1H, J = 7.3 Hz, CH^{Ar}), 2.98 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 177.3 (N=C), 153.3 ($C^{Ar\text{-}q}$), 139.8 ($C^{Ar\text{-}q}$), 137.7 ($C^{Ar\text{-}q}$), 133.5 ($C^{Ar\text{-}q}$), 131.9 (2CH^{Ar}), 130.1 (CH^{Ar}), 130.0 ($C^{Ar\text{-}q}$), 129.9 (2CH^{Ar}), 129.0 (CH^{Ar}), 127.2 (CH^{Ar}), 126.3 ($C^{Ar\text{-}q}$), 125.9 (2CH^{Ar}), 123.4 (CH^{Ar}), 121.6 (CH^{Ar}), 92.9 (OC^q), 52.6 (OCH_3); IR ($CHCl_3$): ν = 1693 (N=C), 1085 (C–O); HR-MS (ES): m/z = 412.0115, calcd. for $C_{21}H_{16}BrClNO$ $[M+H]^+$: 412.0098.

3-Methoxy-2,3-diaryl-3*H*-indole (6aeb): From 30 mg (0.14 mmol) of TMS-azide **4a-Si**, and after chromatography of the residue using hexanes/Et_2O (97:3) containing NEt_3 (2%) as eluent, gave compound **6aeb** as a yellow oil; yield: 33 mg (57%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.04 (m, 2H, 2CH^{Ar}), 7.38 (d, 1H, J = 7.7 Hz, CH^{Ar}), 7.38 (m, 5H, 5CH^{Ar}), 7.21 (m, 3H, 3CH^{Ar}), 7.11 (d, 1H, J = 7.3 Hz, CH^{Ar}), 3.07 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 177.1 (N=C), 153.3 ($C^{Ar\text{-}q}$), 139.7 ($C^{Ar\text{-}q}$), 138.3 ($C^{Ar\text{-}q}$), 137.7 ($C^{Ar\text{-}q}$), 131.9 (2CH^{Ar}), 130.1 (CH^{Ar}), 129.7 (2CH^{Ar}), 129.6 ($C^{Ar\text{-}q}$), 128.9 (2CH^{Ar}), 127.1 (CH^{Ar}), 126.2 (2CH^{Ar}), 123.4 (CH^{Ar}), 121.6 ($C^{Ar\text{-}q}$), 121.5 (CH^{Ar}), 92.9 (OC^q), 52.6 (OCH_3).; IR ($CHCl_3$): ν = 1726 (N=C), 1087 cm^{-1} (C–O); HR-MS (ES): m/z = 412.0087, calcd. for $C_{21}H_{16}BrClNO$ $[M+H]^+$: 412.0098.

General Procedure for the Base-Catalyzed Rearrangement Reaction of 3-Methoxy-2,3-diaryl-3*H*-indoles 6; Preparation of 2,3-Diaryl-1*H*-indoles 5

A solution of the corresponding 3*H*-indole 6 (1 mmol) in ethanolic potash (115 mL, KOH 1M in EtOH) was stirred under microwave heating (105 °C) until the complete disappearance of the starting material (TLC, typically 12 h). After this time, the reaction mixture was cooled down to 0 °C and neutralized with HCl (3M) until pH 7. The aqueous phase was extracted with EtOAc (3×20 mL), the organic phases were combined, dried over $MgSO_4$ and the solvent removed by distillation under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **5**.

2,3-Diaryl-1*H*-indole (5ab): From 20 mg (0.043 mmol) of 3*H*-indole **6ab**, and after chromatography of the residue using hexanes/DCM (8:2) as eluent, gave compound **5ab** as a colourless solid; yield: 13 mg (71%); mp 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.21 (s, 1H, NH), 7.62 (d, 1H, J = 7.9 Hz, CH^{Ar}), 7.47 (m, 5H, 5CH^{Ar}), 7.27 (m, 5H, 5CH^{Ar}), 7.17 (m, 1H, CH^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 135.9 ($C^{Ar\text{-}q}$), 133.7 ($C^{Ar\text{-}q}$), 133.0 ($C^{Ar\text{-}q}$), 132.0 (2CH^{Ar}), 131.8 (2CH^{Ar}), 131.6 (2CH^{Ar}), 131.2 ($C^{Ar\text{-}q}$), 129.6 (2CH^{Ar}), 128.3 ($C^{Ar\text{-}q}$), 123.2 (CH^{Ar}), 122.1 ($C^{Ar\text{-}q}$), 120.8 (CH^{Ar}), 120.4 ($C^{Ar\text{-}q}$), 119.4 (CH^{Ar}), 114.3 ($C^{Ar\text{-}q}$), 111.0 (CH^{Ar}); IR ($CHCl_3$): ν = 3417 cm^{-1} (N–H); HR-MS (ES): m/z = 425.9484, calcd. for $C_{20}H_{14}Br_2N$ $[M+H]^+$: 425.9487.

General Procedure for the Acid-Catalyzed Rearrangement Reaction of 3-Methoxy-2,3-diaryl-3*H*-indoles 6; Preparation of 2-Oxindoles 8

A solution of the corresponding 3*H*-indole **6** (1 mmol) in ethanolic sulfuric acid (115 mL, H_2SO_4 0.4 M in EtOH) was stirred under microwave heating (125 °C) until the complete disappearance of the starting material (TLC, typically 12 h). After this time, the reaction mixture was cooled down to 0 °C and neutralized with $NaHCO_3$ (aqueous saturated solution) until pH 7. The aqueous phase was extracted with EtOAc (3×10 mL), the organic phases were combined, dried over $MgSO_4$ and the solvent removed by distillation under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **8**.

3,3-Diaryl-2-oxindole (8ab): From 20 mg (0.043 mmol) of 3*H*-indole **6ab**, and after chromatography of the residue using hexanes/AcOEt (97:3→80:20) as eluent, gave compound **8ab** as a colourless oil; yield: 14 mg (72%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.48 (s, 1H, NH), 7.44 (m, 4H, 4 CH^{Ar}), 7.28 (t, 1H, J = 7.6 Hz, CH^{Ar}), 7.16 (m, 5H, 5 CH^{Ar}), 7.09 (t, 1H, J = 7.6 Hz, CH^{Ar}), 6.98 (d, 1H, J = 7.8 Hz, CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 178.8 (C=O), 140.2 (2 $C^{Ar\text{-}q}$), 139.9 ($C^{Ar\text{-}q}$), 132.4 ($C^{Ar\text{-}q}$), 131.7 (4 CH^{Ar}), 130.1 (4 CH^{Ar}), 128.8 (CH^{Ar}), 126.1 (CH^{Ar}), 123.2 (CH^{Ar}), 121.9 (2 $C^{Ar\text{-}q}$), 110.5 (CH^{Ar}), 61.0 (C^q–C=O); IR ($CHCl_3$): ν = 3222 (N–H), 1711 cm^{-1} (C=O); HR-MS (ES): m/z = 441.9446, calcd for $C_{20}H_{14}Br_2NO$ $[M+H]^+$: 441.9437.

General Procedure for the Acid-Catalyzed Rearrangement Reaction of 3-Methoxy-2,3-diaryl-3*H*-indoles 6; Preparation of 3-oxindolines 9

A solution of the corresponding 3*H*-indole **6** (1 mmol) in ethanolic sulfuric acid (115 mL, H_2SO_4 0.2 M in EtOH) was stirred under microwave heating (95 °C) until the complete disappearance of the starting material (TLC, typically 12 h). After this time, the reaction mixture was cooled down to 0 °C and neutralized with $NaHCO_3$ (aqueous saturated solution) until pH 7. The aqueous phase was extracted with EtOAc (3×10 mL), the organic phases were combined, dried over $MgSO_4$ and the solvent removed by distillation under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **9** along with compounds **8** as minor components.

2,2-Diaryl-3-oxindoline (9ab): From 20 mg (0.043 mmol) of 3*H*-indole **6ab**, and after chromatography of the residue using hexanes:AcOEt (97:3) as eluent, gave compound **9ab** as a yellow oil; yield: 10 mg (51%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, 1H, J = 7.7 Hz, CH^{Ar}), 7.53 (t, 1H, J = 7.7 Hz, CH^{Ar}), 7.46 (m, 4H, 4 CH^{Ar}), 7.25 (m, 4H, 4 CH^{Ar}), 6.94 (m, 2H, 2 CH^{Ar}), 5.09 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 199.8 (C=O), 159.9 ($C^{Ar\text{-}q}$), 139.7 (2 $C^{Ar\text{-}q}$), 138.0 (CH^{Ar}), 131.8 (4 CH^{Ar}), 129.1 (4 CH^{Ar}), 125.6 (CH^{Ar}), 122.4 (2 $C^{Ar\text{-}q}$), 120.3 (CH^{Ar}), 119.8 ($C^{Ar\text{-}q}$), 112.7 (CH^{Ar}), 74.0 (NC^q); IR ($CHCl_3$): ν = 3450 (N–H), 1686 cm^{-1} (C=O); HR-MS (ES): m/z = 441.9453, calcd. for $C_{20}H_{14}Br_2NO$ $[M+H]^+$: 441.9437.

General Procedure for the Photopromoted Gold-Catalyzed Monoarylation Reaction of Aryl-Terminated Alkynones 14-Ph or 16-Ph with Diazonium Salts 2; Preparation of 3-Arylflavones 15 and 3-Arylthioflavones 17

In a Schlenk tube in the absence of light at −78 °C under an argon atmosphere, Ph_3PAuCl (10 mol%) and $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arenediazonium salt **2** (3.0 equiv.) in a mixture of MeOH/MeCN (3:1, 3 mL). Then, a solution of the appropriate aryl-terminated alkynone **14-Ph** or **16-Ph** (1.0 mmol) in MeOH/MeCN (3:1, 2.5 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 5 min. The reaction mixture was then warmed to room temperature and stirred under irradiation from a visible light source (21 W fluorescent light bulb installed in a tool box). After disappearance of the starting material (TLC), the reaction mixture was concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **15** and **17** are given in the following paragraphs.

3-Arylflavone (15c): From 21 mg (0.10 mmol) of aryl-terminated alkynone **14-Ph**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **15c** as a colourless solid; yield: 24 mg (66%); mp 127–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.32 (dd, 1H, J = 7.6 Hz, J = 1.5 Hz, CH^{Ar}), 8.00 (d, 2H, J = 8.3 Hz, 2 CH^{Ar}), 7.77–7.71 (m, 1H, 1 CH^{Ar}), 7.56 (d, 1H, J = 8.6 Hz, 1 CH^{Ar}), 7.49–7.27 (m, 8H, 8 CH^{Ar}), 4.38 (q, 2H, J = 6.5 Hz, CH_2), 1.40 (t, 3H, J = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 176.8 (C=O), 166.4 (C=O), 161.8 (C=C), 155.9 ($C^{Ar\text{-}q}$), 137.8 ($C^{Ar\text{-}q}$), 133.8 (CH^{Ar}), 132.8 ($C^{Ar\text{-}q}$), 131.3 (2 CH^{Ar}), 130.3 (CH^{Ar}), 129.5 (2 CH^{Ar}), 129.4 ($C^{Ar\text{-}q}$), 129.3 (2 CH^{Ar}), 128.2 (2 CH^{Ar}), 126.3 (CH^{Ar}), 125.2 (CH^{Ar}), 123.3 ($C^{Ar\text{-}q}$), 122.1 ($C^{Ar\text{-}q}$), 118.0 (CH^{Ar}), 60.9 (CH_2), 14.3 (CH_3); IR ($CHCl_3$): ν = 1712 (C=O), 1639 cm^{-1} (C=O), 1270; HR-MS (ES): m/z = 371.12826, calcd. for $C_{24}H_{19}O_4$ $[M+H]^+$: 371.1278.

3-Arylflavone (15f): From 21 mg (0.10 mmol) of aryl-terminated alkynone **14-Ph**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **15f** as a colourless solid; yield: 25 mg (69%); mp 144–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.31 (dd, 1H, J = 7.6 Hz, J = 1.5 Hz, CH^{Ar}), 7.76–7.73 (m, 2H, 2 CH^{Ar}), 7.57 (d, 1H, J = 8.6 Hz, CH^{Ar}), 7.49–7.46 (m, 1H, 1 CH^{Ar}), 7.40–7.31 (m, 5H, 5 CH^{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 176.8 (C=O), 162.1 (C=C), 159.0 ($C^{Ar\text{-}q}$), 136.8 ($C^{Ar\text{-}q}$), 134.0 (CH^{Ar}), 131.7 (2 CH^{Ar}), 130.5 (CH^{Ar}), 129.5 (2 CH^{Ar}), 129.6 (q, $J_{C,F}$ = 32.0 Hz, $C^{Ar\text{-}q}$), 128.3 (2 CH^{Ar}), 126.5 (CH^{Ar}), 125.4 (CH^{Ar}), 125.4 (q, $J_{C,F}$ = 4.3 Hz, 2 CH^{Ar}), 124.1 (q, $J_{C,F}$ = 272.0 Hz, CF_3), 123.3 ($C^{Ar\text{-}q}$), 121.7 ($C^{Ar\text{-}q}$), 118.0(CH^{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −62.9 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1638 (C=O), 1377 cm^{-1}; HR-MS (ES): m/z = 367.0947, calcd. for $C_{22}H_{14}F_3O_2$ $[M+H]^+$: 367.0904.

3-Arylthioflavone (17b): From 35 mg (0.14 mmol) of aryl-terminated alkynone **16-Ph**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **17b** as a colourless solid; yield: 33 mg (61%); mp 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C):

$\delta = 8.50$ (d, 1H, $J = 7.7$ Hz, CH^{Ar}), 7.52 (m, 3H, $3\,CH^{Ar}$), 7.20 (m, 7H, $7\,CH^{Ar}$), 6.91 (m, 2H, $2\,CH^{Ar}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 179.2$ (C=O), 150.8 (C=C), 137.2 ($C^{Ar\text{-}q}$), 136.6 ($C^{Ar\text{-}q}$), 134.5 ($C^{Ar\text{-}q}$), 134.4 (C=C), 132.8 ($2\,CH^{Ar}$), 131.6 (CH^{Ar}), 131.1 ($C^{Ar\text{-}q}$), 130.9 ($2\,CH^{Ar}$), 129.5 (CH^{Ar}), 129.3 (CH^{Ar}), 129.2 ($2CH^{Ar}$), 128.5 ($2\,CH^{Ar}$), 127.8 (CH^{Ar}), 125.8 (CH^{Ar}), 121.4 ($C^{Ar\text{-}q}$); IR ($CHCl_3$): $\nu = 1617$ (C=O), 1589 cm^{-1} (C=C); HR-MS (ES): $m/z = 392.9935$ calcd. for $C_{21}H_{14}BrOS$ $[M+H]^+$: 392.9943.

3-Arylthioflavone (17e): From 31 mg (0.12 mmol) of aryl-terminated alkynone **16-Ph**, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent, gave compound **17e** as a colourless solid; yield: 28 mg (68%); mp 154–156 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.58$ (d, 1H, $J = 7.8$ Hz, CH^{Ar}), 7.62 (m, 3H, $3\,CH^{Ar}$), 7.28 (m, 3H, $3\,CH^{Ar}$), 7.21 (m, 4H, $4\,CH^{Ar}$), 7.05 ($2\,CH^{Ar}$); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 179.3$ (C=O), 150.8 (C=C), 137.2 ($C^{Ar\text{-}q}$), 136.6 ($C^{Ar\text{-}q}$), 134.4 ($C^{Ar\text{-}q}$), 134.0 (C=C), 133.1 ($C^{Ar\text{-}q}$), 132.5 ($2\,CH^{Ar}$), 131.6 (CH^{Ar}), 131.2 ($C^{Ar\text{-}q}$), 129.6 (CH^{Ar}), 129.3 (CH^{Ar}), 129.2 ($2\,CH^{Ar}$), 128.5 ($2\,CH^{Ar}$), 128.0 ($2\,CH^{Ar}$), 127.8 (CH^{Ar}), 125.8 (CH^{Ar}); IR ($CHCl_3$): $\nu = 1617$ (C=O), 1588 cm^{-1} (C=C); HR-MS (ES): $m/z = 349.0457$, calcd. for $C_{21}H_{13}ClOS$ $[M+H]^+$: 349.0448.

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[16] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. This contains compound characterization data, experimental procedures, and copies of NMR spectra for all new compounds.

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Advanced Synthesis & Catalysis

Gold-Photoredox-Cocatalyzed Tandem Oxycyclization/Coupling Sequence of Allenols and Diazonium Salts with Visible Light Mediation

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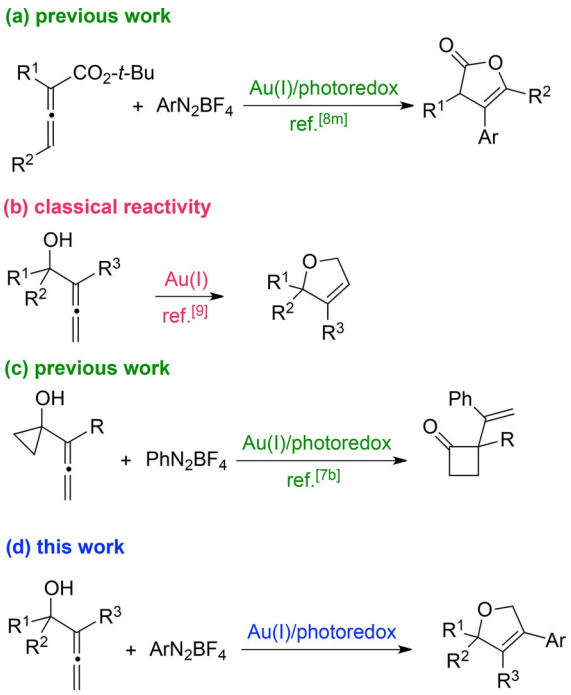
Abstract: The room temperature radical cycloetherification/arylation cascade of allenols and diazonium salts has been accomplished *via* a combination of gold and photoredox catalysis to provide 2,3,4-trisubstituted-2,5-dihydrofurans. The functionalized oxacycle formation sequence is chemo- and regioselective for the cycloetherification and for the position that bears the aryl moiety after the cross-coupling. Mechanistic investigations revealed that this transformation proceeds through an initial oxidation of gold(I) to a phenyl gold(III) complex, which, upon coordination to the allene, catalyzes its cyclization and leads to the coupling product after a reductive elimination regenerating Au(I).

Keywords: allenes; cyclization; density functional calculations; gold; synthetic methods

Introduction

Because of their powerful soft Lewis acidic nature, gold complexes have been used extensively by the synthetic community in carbo- and hetero-cyclizations across an unsaturated moiety.[1] Hydrofunctionalization products are normally obtained through a final protodeauration step. However, the use of redox gold catalysis in tandem cyclization/coupling sequences has been precluded due to the high redox potential between Au(I) and Au(III).[2] In order to achieve C–C coupling rather than only a protodeauration, a transmetalation from the vinylgold(I) intermediates to palladium(II),[3] iron and ruthenium[4] was investigated. But it was discovered that the transmetalation is only exergonic if at the same time a halide is transferred to gold,[5] which then blocks the gold catalyst after the first turnover. The addition of strong oxidants has allowed for the implementation of Au(I)/Au(III) cycles in coupling reactions.[6] However, the use of superstoichiometric amounts of environmentally non-benign oxidants remains a major drawback of the latter approaches. Independently, Glorius[7a] and Toste[7b] have successfully introduced the combination of gold and photoredox catalysis.[8] In this context, Shin described the intramolecular oxyarylation of allenoates (Scheme 1a).[8m] Despite the fact that gold complexes have shown specific catalytic activity in allenol chemistry for the formation of unsubstituted oxacycles (Scheme 1b),[9] the joint use of gold and photoredox catalysis has been reported to result in the arylative ring expansion of cyclopropyl allenols (Scheme 1c).[7b] Consequently, efficient gold-photoredox-cocatalyzed synthesis of functionalized oxacycles with high chemo- and regioselectivity from allenols remains a challenge. Herein we wish to report a tandem sequence of allenol oxycyclization/aryldiazonium salt cross-coupling for the controlled direct preparation of substituted dihydrofurans under mild conditions (Scheme 1d). Besides, density functional theory (DFT) calculations were performed to obtain an insight into various aspects of the controlled reac-



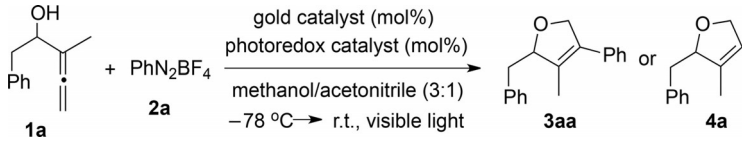
Scheme 1. Gold-catalyzed reactions of allenoates and allenols.

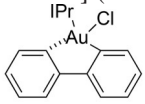
tivity of allenols under gold-photoredox catalysis, especially the order in which the key steps (gold oxidation, allene cyclization and reductive elimination) take place.

Results and Discussion

We first screened aryldiazonium salts and reaction conditions suitable for the allenol cycloetherification/cross-coupling process. With this idea in mind, the reaction of allenol **1a** with diazonium salt **2a** was examined under several reaction conditions using a 21 W compact fluorescent lamp (CFL) as the light source. Initially, we tried the tandem sequence on allenol **1a** by using PhN_2BF_4 **2a** as the arylating reagent, the Gagosz catalyst $[(Ph_3P)AuNTf_2]$,[10] and the photoactive ruthenium complex $[Ru(bpy)_3](PF_6)_2$ (bpy = 2,2′-bipyridine), in the presence of visible light. Interestingly, the reaction proceeded rapidly; however, this experiment gave the desired adduct **3aa** as the minor product together with a considerable amount of the cycloisomerization adduct **4a** (Table 1, entry 1). The formation of non-desired adduct **4a** could be ascribed to the poor coordinating capability of the triflimide anion, which liberates in solution cationic gold(I) from Gagosz' catalyst and avoids the reaction with the diazonium salt. Encouraged by this promising result and aiming to eliminate the oxycyclization/protodeauration path, we next examined the one-pot oxycyclization/arylation of allenol **1a** using different gold salts. $AuCl_3$ was tested, but it failed to catalyze the coupling reaction (Table 1, entry 2). Fortunately, $(Ph_3P)AuCl$ serves as an excellent catalyst for this tandem sequence. In the presence of $(Ph_3P)AuCl$, the reaction of allenol **1a** with phenyldiazonium salt **2a**

Table 1. Selective oxycyclization/arylation of allenol **1a** under modified gold-photoredox-cocatalyzed conditions. Effect of reaction conditions on product distribution.

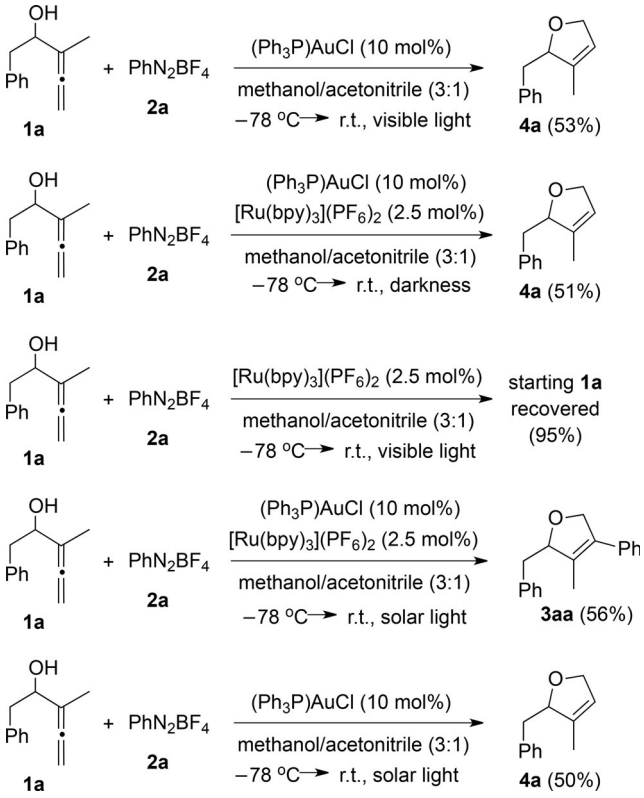


Entry	Gold Catalyst	Photocatalyst[a]	Time [h][b]	Yield [%][c]
1	$[(Ph_3P)AuNTf_2]$ (10 mol%)	[Ru]	2	**3aa** (17)/**4a** (20)
2	$AuCl_3$ (10 mol%)	[Ru]	3	**4a** (50)
3	$[(PPh_3)AuCl]$ (15 mol%)	[Ru]	1	**3aa** (77)
4	$[(PPh_3)AuCl]$ (10 mol%)	[Ru]	1	**3aa** (77)
5	$[(PPh_3)AuCl]$ (5 mol%)	[Ru]	1	**3aa** (47)
6	$[(PPh_3)AuCl]$/AgOTf (10 mol%)	[Ru]	1	**3aa** (20)
7	[IPrAuCl] (15 mol%)	[Ru]	24	**4a** (10)
8	 Toste Au(III) complex	[Ru]	48	–
9	$[(PPh_3)AuCl]$ (15 mol%)]	[Ir]	1.5	**3aa** (73)
10	$[(PPh_3)AuCl]$ (15 mol%)	fluorescein	3	**4a** (38)

[a] [Ru] = $[Ru(bpy)_3](PF_6)_2$. [Ir] = $[Ir(ppy)_2(dtbbpy)](PF_6)_2$.
[b] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate diazonium salt, which became amber and finally black.
[c] Yield of pure, isolated product with correct analytical and spectral data.

occurred smoothly at room temperature in one hour to afford dihydrofuran **3aa** in 77% yield, regardless of the amount of ruthenium-based catalyst (Table 1, entries 3 and 4). Presumably, the elimination of the cycloisomerization path should be attributed to the coordinatively saturated nature of this gold complex, which may force a prior activation *via* arylgold(III) species. The optimal amount of gold catalyst was established at 10 mol% with a ratio Au(I) salt/Ru(II) salt of 4:1 (Table 1, entry 4). A lower loading of catalyst had the effect of lowering the conversion for a fixed reaction time as well as the final yield of heterocycle **3aa** (Table 1, entry 5). The addition of a silver additive to $(Ph_3P)AuCl$ resulted in considerable yield reduction of adduct **3aa** (Table 1, entry 6). Other Au-based catalysts were less effective. Allenol **1a** reacted only slowly with the Au(I) salt [AuClIPr] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] to give exclusively dihydrofuran **4a**, which was obtained in substantially decreased yield (Table 1, entry 7). The Toste Au(III) complex[11] led to a complicated mixture in which some starting allenol **1a** remained unreacted, not allowing the isolation of dihydrofuran **3aa** even in a minimal yield (Table 1, entry 8). In a screening of photoredox catalysts, $[Ir(ppy)_2(dtbbpy)](PF_6)_2$ (ppy = 2-phenylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) delivered adduct **3aa** in a slightly lower yield (Table 1, entry 9), while the use of fluorescein resulted in cycloisomerization adduct **4a** (Table 1, entry 10). An excess (3 equiv.) of diazonium salt was chosen as the most efficient amount of arylating reagent. A survey of solvents revealed that the reaction is best performed in a mixture (3:1) of methanol/acetonitrile. Diminished yields and recovery of starting allenol **1a** were detected when using MeOH/MeCN (1:1), water/MeCN (1:1), MeCN, DMF, or DMF/water (1:1).

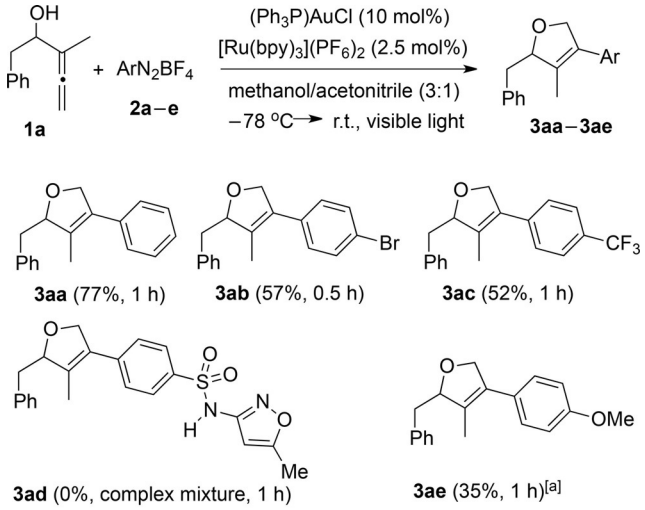
To clarify the active participation of the gold catalyst and the photosensitizer in the transformation, some control experiments were carried out using allenol **1a**. Insight into the direct participation of the photoredox catalyst in the metal-catalyzed process was obtained by running an experiment without the addition of $[Ru(bpy)_3](PF_6)_2$ (under otherwise identical conditions), because the cycloisomerization adduct **4a** was exclusively achieved (Scheme 2). There was no evidence of the presence of type **3aa** products. The critical role of the gold salt in the tandem sequence was demonstrated when more of the starting allene **1a** remained unreacted in the absence of $(Ph_3P)AuCl$ (Scheme 2). Consequently, a synergistic catalysis of gold and photosensitizer for this redox cyclization/coupling sequence may be inferred.[12] Interestingly, solar light also promoted the oxycyclization/arylation of allenol **1a** with diazonium salt **2a**. Indeed, adduct **3aa** was obtained in a reasonable yield (56%) when the reaction flask was exposed to solar light for 10 h on a sunny day (Scheme 2). Taking into consideration



Scheme 2. Control experiments.

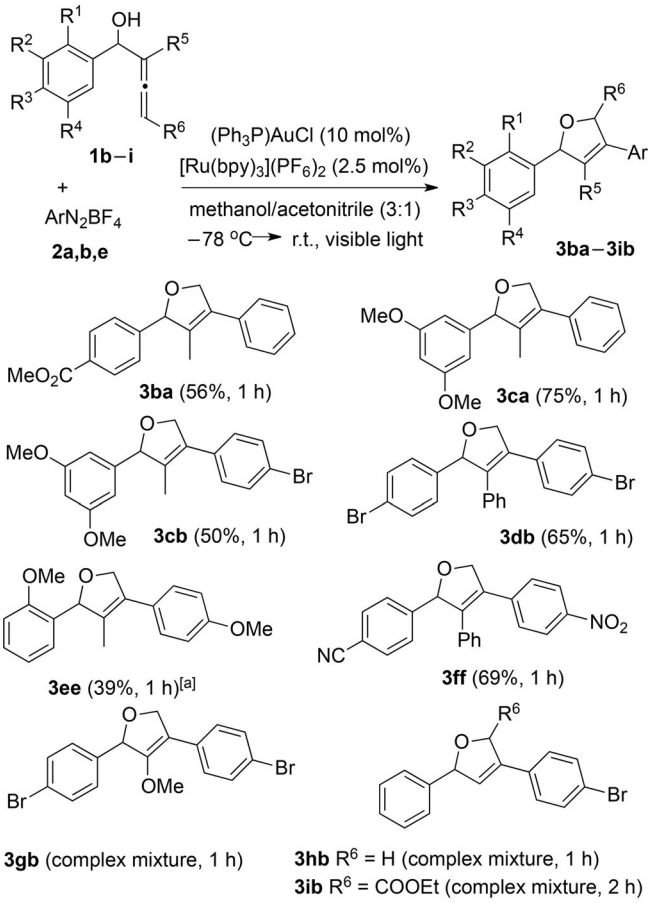
that irradiation with UVA could generate an aryl radical from the diazo compound without the need of a photocatalyst, a control experiment using daylight with the gold salt was carried out. However, non-arylated adduct **4a** was obtained (Scheme 2).

Having identified the optimized reaction conditions, we proceeded to study the aryldiazonium salt scope to further expand the synthetic utility of the process (Scheme 3). Several substituents such as trifluoromethyl, bromide, and methoxy were well tolerated. Interestingly, the carbon-bromide bond in **3ab** was not affected and could serve as reactive handle for further elaboration. The steric properties of the substituents in the arene moiety did affect significantly the coupling, because the reaction between allenol **1a** and the *ortho*-substituted salt 2-bromobenzenediazonium tetrafluoroborate did not yield the arylated dihydrofuran. Besides, the electronic nature of the substituents has a strong influence on the course of the reaction. Compared to aryldiazonium salts bearing electron-donating groups, diazo derivatives having electron-withdrawing substituents gave better results as far as both yields and selectively are concerned. Thus, the electron-rich 4-methoxyphenyldiazonium salt **2e** afforded in modest yield as main product the 2,3,4-trisubstituted-2,5-dihydrofuran **3ae**, together with the 2,3-disubstituted-2,5-dihydrofuran **4a**. Unfortunately, the complex diazonium salt **2d** derived



[a] 2,3-Disubstituted-2,5-dihydrofuran **4a** was formed in 8% yield as minor product (ratio **3ae/4a** = 75:25).

Scheme 3. Selective oxycyclization/arylation of allenol **1a** with functionalized aryldiazonium salts under gold-photoredox-cocatalyzed conditions.



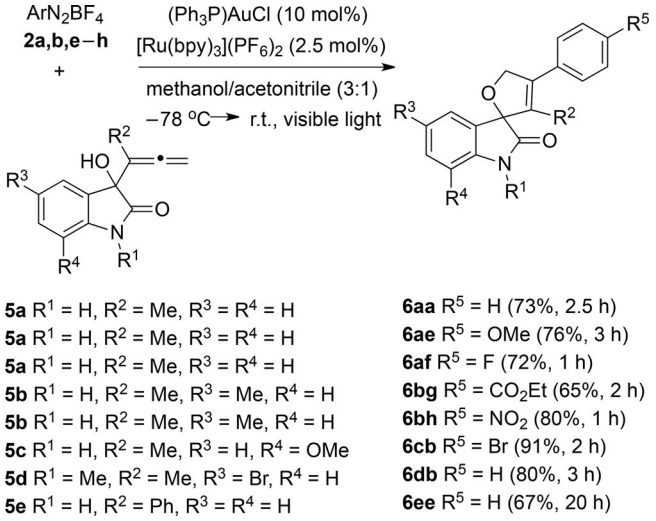
[a] 2,3-Disubstituted-2,5-dihydrofuran **4e** was formed in 14% yield as chromatographically separable minor product.

Scheme 4. Gold-photoredox-cocatalyzed reaction of allenols **1b–i** with aryldiazonium salts **2**. Controlled synthesis of trisubstituted dihydrofurans **3ba–3ff**.

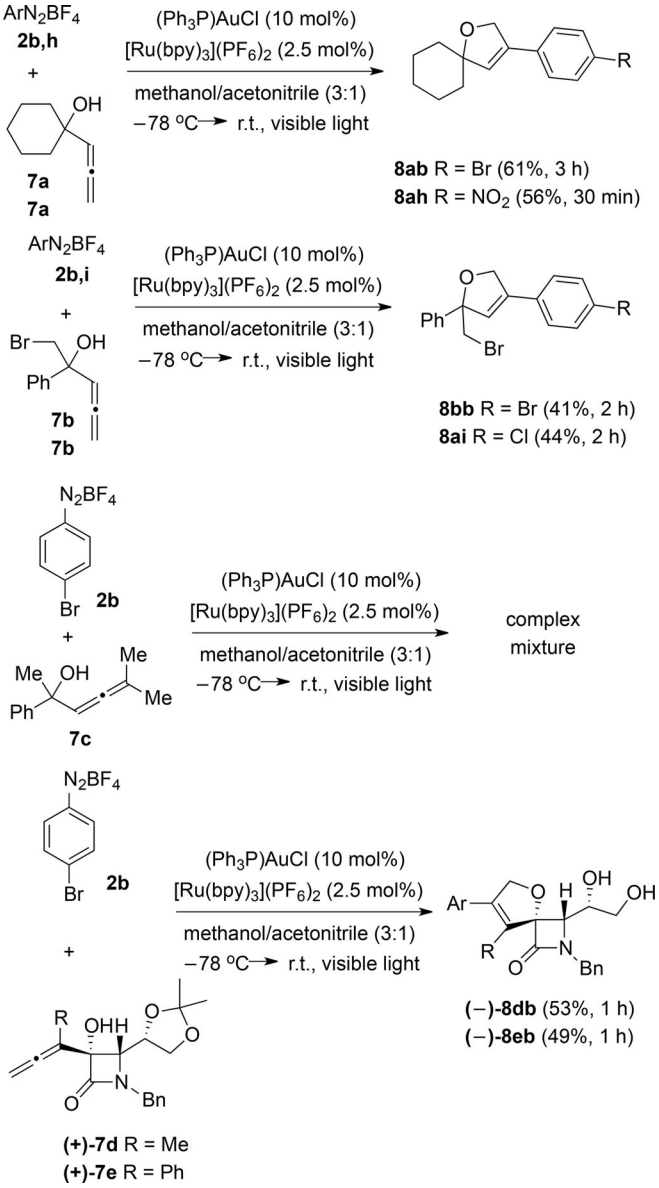
from the antibiotic sulfamethoxazole could not be successfully used in this cyclization/coupling process.

With the optimized catalyst combination in hand, the generality of this allenic oxycyclization/coupling sequence was explored with respect to the allenol through the investigation of the effect of diverse substituents on the allene substrate. We were pleased to find that the scope could be extended from aliphatic- (**1a**) to aromatic-based (**1b–f**) allenol systems. A wide variety of easily available allenols were utilized and most of them were found to be viable precursors, allowing access to the corresponding functionalized oxacycles. As summarized in Scheme 4, the reactions proceeded smoothly at room temperature with a wide variety of 2,3-dien-1-ols, irrespective of their electronic properties and substitution patterns at the arene, to give trisubstituted dihydrofurans **3ba–3ff** in good yields (Scheme 4). Furthermore, the transformation is not restricted to methyl-substituted allenols but is also applicable to allenols with aromatic substituents (**1d** and **1f**). The reaction is insensitive to the steric effect on allenols, since comparable results were observed when a phenyl group was present in the allene moiety (**3db** and **3ff**). Nevertheless, methoxyallene **1g** and allenes **1h**, **i** lacking substitution at the proximal position were poor participants and only complicated reaction mixtures were observed. From the examples above (allenols **1h** and **1i**) it can be inferred that distal substitution of the allenol is not welcome.

Despite the fact that the palladium-catalyzed arylation/spirocyclization of oxindole-tethered allenols has been previously resulted in failure,[13] we decide to test the dual gold-photoredox catalyzed reaction of allenols **5** with aryldiazonium salts **2**. Notably, as depicted in Scheme 5 spirocyclic compounds **6aa–6ee** were smoothly obtained in good to excellent yields using the catalytic system $(Ph_3P)AuCl$ (10 mol%)/$[Ru(bpy)_3](PF_6)_2$ (2.5 mol%). The presence of substituents with various sizes and electronic demands (H, Br, F, NO_2, CO_2Et, OMe) both at the diazonium salt and oxindole provided the same reactivity pattern. Even the electron-rich 4-methoxyphenyldiazonium salt **2e** provided 2,3,4-trisubstituted-2,5-dihydrofurans **6ae** and **6ee** as exclusive products in reasonable yields. Bromide substitution in products **6cb** and **6db** may be synthetically valuable, offering further functionalization through cross-coupling protocols. As expected, substitution at the nitrogen atom of the heterocycle in *N*-methylallenol **5d** has little effect upon the reactivity of the precursor. Substrate **5e**, a phenyl-substituted allene, was also amenable to these cyclization/arylation conditions, although it showed decreased reactivity and required a prolonged reaction time (20 h). A



Scheme 5. Gold-photoredox-cocatalyzed reaction of allenols **5a–e** with aryldiazonium salts **2**. Controlled synthesis of oxa-spirooxindoles **6aa–6ee**.



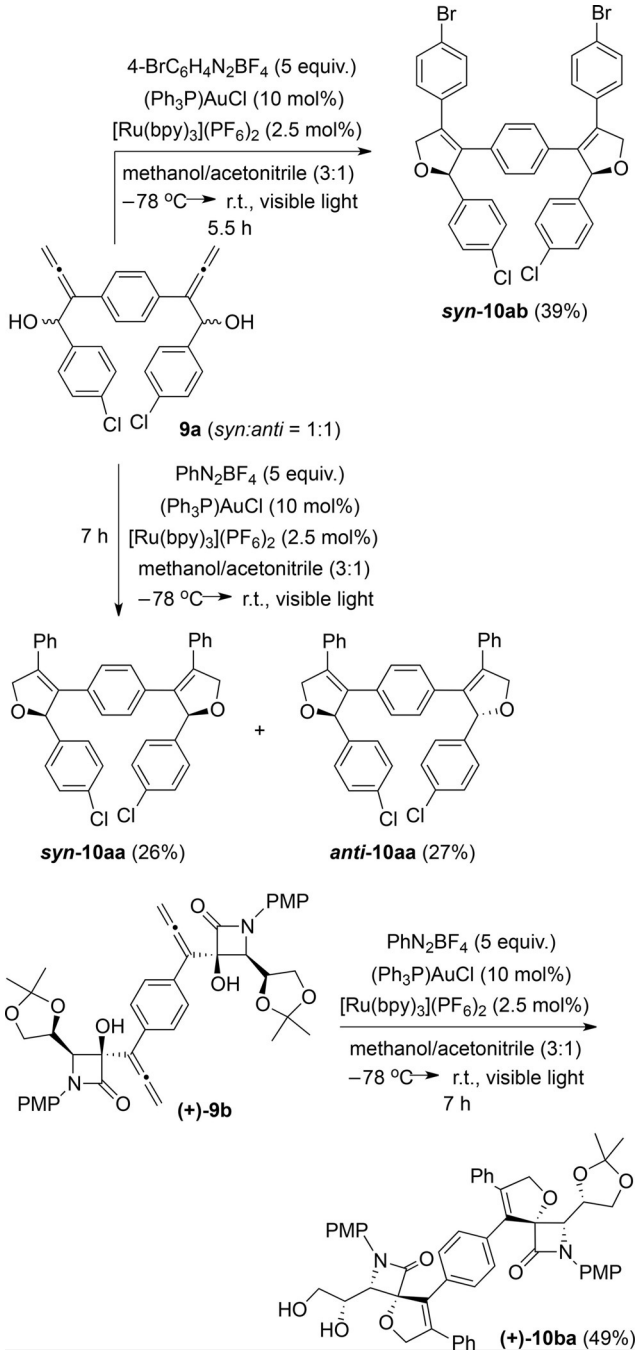
Scheme 6. Gold-photoredox-cocatalyzed reaction of allenols **7** with aryldiazonium salts **2**. Controlled synthesis of oxa-spiro-β-lactams **8**.

further potential advantage of this strategy is highlighted in a scale-up of the process. It is worth noting that no evident loss of yield was observed for adduct **6aa** (isolated yield: 75%) when the reaction was carried out on a 1-gram scale and the gold catalyst loading was reduced from 10 mol% to 5 mol%. It should be noted that adducts **6** belong to the oxa-spirooxindole family, a likely auspicious subgroup of the spirooxindole alkaloids.[14]

Subjection of 1,1,1-trisubstituted 2-unsubstituted buta-2,3-dien-1-ols **7a** and **7b** to the oxycylization/coupling sequence with diazonium salts **2** gave the desired products **8** in fair yields (Scheme 6), thus suggesting that substitution at the internal allene position was not essential to facilitate the heterocyclization/arylation. Unfortunately, compound **7c**, with two methyl substituents at the terminal allenic carbon, only led to multiple uncharacterized products after just 30 min of reaction. Since the above allenols are racemic, we prepared as cyclization precursors the appealing enantiopure allenol-tethered β-lactams **7d** and **7e**. It was found that the gold/ruthenium-cocatalyzed reaction of allenols **7d** and **7e** with aryldiazonium salt **2b** in the presence of visible light, smoothly afforded the desired adducts **8db** and **8eb** (Scheme 6). The gold-photoredox reaction is rapid and totally selective. Remarkably, Scheme 6 shows how the mild conditions of dual gold-photoredox catalysis allow the selective formation of functionalized spirocyclic β-lactams without harming the sensitive 2-azetidinone nucleus. However, cleavage of the ketal moiety was observed. Compounds **8** can be viewed as hybrid scaffolds joining two privileged motifs, the dihydrofuran and β-lactam substructures, through a unique spiro-quaternary carbon. It is worth noting that this method offers an efficient alternative to the existing low-yielding unselective coupling of iodoarenes with allenol-tethered β-lactams for the synthesis of oxaspirocyclic β-lactams.[15]

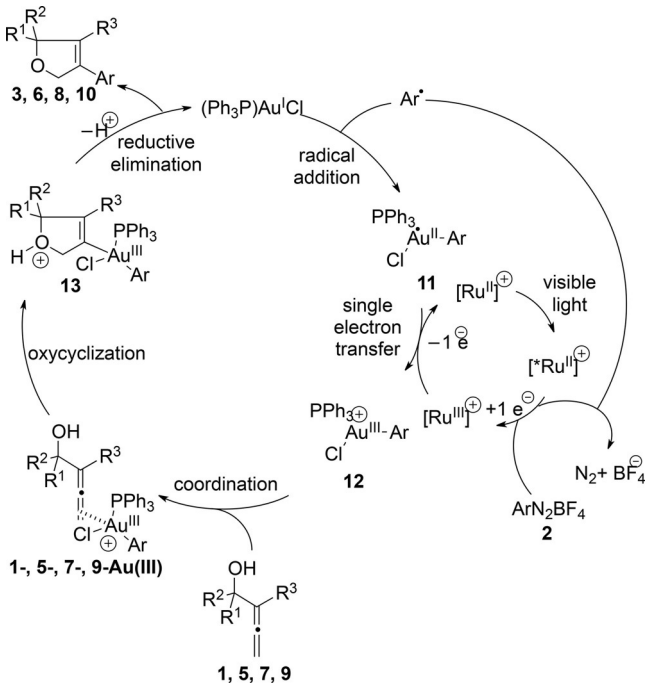
In order to access symmetrically substituted bis(2,3,4-trisubstituted-2,5-dihydrofurans), reaction conditions that would favor the double pathway over single cycloetherification/arylation were examined in bis(allenols) **9**. The investigations were conducted with bis(allenol) **9a**, prepared as a single regioisomer but as an inseparable *syn*/*anti* mixture (1:1),[16] as the cyclization precursor and diazonium salt **2a** as the arylating reagent. Employing 5 equiv. of **2a** under otherwise identical standard conditions led to a 1:1 mixture

of chromatographically separable bis(2,3,4-trisubstituted-2,5-dihydrofurans) *syn*-**10aa** (26% yield) and *anti*-**10aa** (27% yield) (Scheme 7). Next, the two-fold photoredox reaction was accomplished by treatment of **9a** (*syn*/*anti* = 1:1) with diazonium salt **2b**. Surprisingly, bis(2,3,4-trisubstituted-2,5-dihydrofuran) *syn*-**10ab** was isolated as the sole product in 39% yield. Apparently, the double oxycyclization/arylation reaction between bis(allenol) *anti*-**9a** and diazonium salt **2b** was non-productive, allowing for the discriminatory obtention of the *syn*-isomer. The double cycloetherification/arylation photoredox cascade of enantiopure bis(allenol) **9b** into bis(β-lactam-tethered 2,5-dihydrofuran) **10ba** occurs smoothly in a completely selective fashion (Scheme 7). Of particular interest is the exclusive mono-cleavage of one of the ketal moieties under the reaction conditions, allowing differentiation between two chemically equivalent protected diols.



Scheme 7. Gold-photoredox-cocatalyzed two-fold reaction of bis(allenols) **9** with aryldiazonium salts **2**. Controlled synthesis of bis(2,3,4-trisubstituted-2,5-dihydrofurans) **10**.

A conceivable mechanism for the gold-photoredox cocatalyzed formation of oxacycles **3**, **6**, **8**, and **10** from allenols **1**, **5**, **7**, and **9** and diazonium salts **2** is shown in Scheme 8. It may involve the formation of



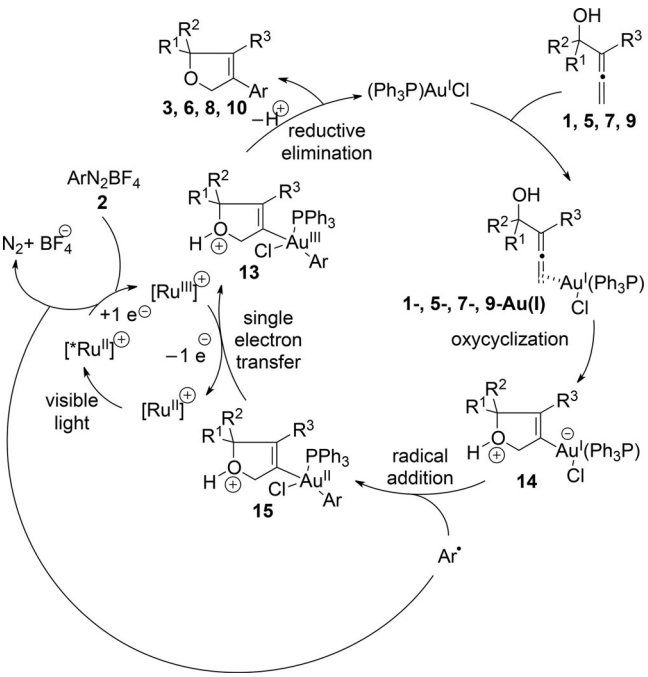
Scheme 8. Mechanistic explanation for the gold-photoredox-cocatalyzed preparation of oxacycles **3**, **6**, **8**, and **10** from allenols **1**, **5**, **7**, and **9** and diazonium salts **2**.

cationic organogold(III) intermediate **12**,[17,18,19] which may be considered as a robust electrophile. Next, arylgold(III) species **12** should interact with the allenol moiety with a final aryl group transfer. A catalytic cycle was postulated based on the use of a Ru(II) species as a strong reductant for the generation of an aryl radical from diazonium salts **2**. Both the short reaction times as well as previous observations from Glorius[20a] in dual gold/photoredox reactions may point to the fact that radical chains may be operating.[20b] Initially, Ru(II) complexes are reversibly promoted to their excited state, $[*Ru(II)]^+$, under visible light exposure. Consecutive transfer of an electron to diazonium salt **2** may generate the corresponding aryl radical, that should be spontaneously paired with the

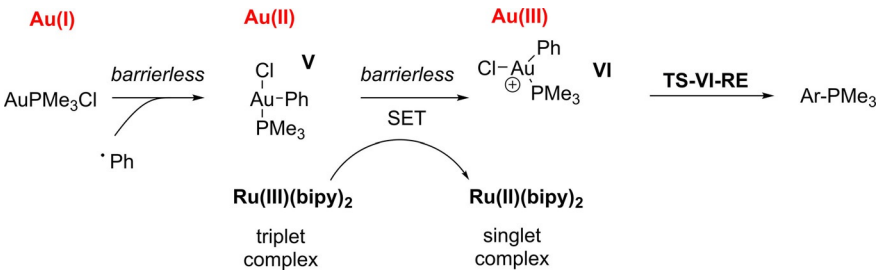
gold(I) salt to form unstable organogold(II) intermediate **11**. Subsequent oxidation by Ru(III) produces arylgold(III) species **12**, releasing the ruthenium(II) photoredox catalyst into the first catalytic cycle (Scheme 8, *right catalytic cycle*). Next, allenols **1**, **5**, **7**, and **9** enter the second catalytic cycle, which is gold-catalyzed, furnishing complex **1-**, **5-**, **7-**, and **9**-Au(III) through coordination of the gold salt to the external allenic double bond. Species **1-**, **5-**, **7-**, and **9**-Au(III) undergo a regioselective intramolecular 5-*endo*-trig oxycyclization reaction to produce the oxacyclic alkenylgold(III) **13**. Reductive elimination linked to proton release liberates oxacycles **3**, **6**, **8**, and **10** with concomitant regeneration of the gold(I) catalyst, closing the second catalytic cycle (Scheme 8, *left catalytic cycle*).

We also suggest that another possible mechanism proceeds through oxidation of alkenylgold(I) to alkenylgold(III) intermediates by the action of aryl radicals, generated from aryldiazonium salts in the presence of visible light and the photosensitizer. In this mechanistic picture (Scheme 9), the catalytic achievement of oxacycles **3**, **6**, **8**, and **10** may proceed through initial η-coordination of the gold(I) to the distal double bond of allenols **1**, **5**, **7**, and **9** leading to species **1**-Au(I). Next, 5-*endo*-trig alkoxyauration forms cationic oxacycles **14**, which react with the aryl radical to form the oxacyclic alkenylgold(II) **15**. Species **15** enters the second catalytic cycle (Scheme 9, *left catalytic cycle*), which is ruthenium-catalyzed, giving rise to oxacyclic alkenylgold(III) **13** and regenerating the ruthenium(II) catalyst. Loss of proton in species **13** followed by reductive elimination liberates oxacycles **3**, **6**, **8**, and **10** with concomitant regeneration of $(Ph_3P)AuCl$, closing the golden catalytic cycle (Scheme 9, *right catalytic cycle*).

We have used density functional theory (DFT) to study the mechanism of this transformation, with the aim of establishing the preferred sequence for its key steps. The main question is whether the radical addition to the Au(I) center proceeds before or after coordination with the allene and, as a consequence, whether the cyclization takes place on an Au(I) or an Au(III) complex. It seems convenient to start our discussion with the sequence of reactions depicted in Scheme 10, where the Au(I) catalyst, $AuPMe_3Cl$ is oxidized to Au(III), because this part of the mechanism, would be common to all substrates. We propose for this process a two-step mechanism where Au(I) is first oxidized to Au(II) through the addition of a phenyl radical ligand. We found this process to be barrierless, due to our inability to find a transition state between $AuPMe_3Cl$ and **V**. This conclusion was confirmed through the steadily increasing energy upon elongation of the Au–Ph distance in **V** (see the Supporting Information). The resultant Au(II) complex **V**, is only 1.0 kcal mol^{-1} higher in energy than the separate reactants and is proposed to proceed to Au(III) complex **VI** through a single electron transfer (SET) event from a tris(bipyridine)ruthenium(III) complex.



Scheme 9. Alternative mechanistic explanation for the gold-photoredox-cocatalyzed preparation of oxacycles **3**, **6**, **8**, and **10** from allenols **1**, **5**, **7**, and **9** and diazonium salts **2**.



Scheme 10. Oxidation of the original Au(I) complex by addition of a Ph radical and single electron transfer from $Ru(bipy)_3$.[3] The barrier for the reductive elimination on intermediate **VI** is low (2.2 kcal mol^{-1}) and explains the presence of the aryl-phospine coupling product among the reaction products.

To estimate the activation energy corresponding to this SET we have used the Marcus theory,[21] which considers that the barrier associated with such a process is mainly related to the changes on the structure of the reactants and the reorganization of the solvent upon the transfer of an electron from one fragment to the other, according to the following expression:

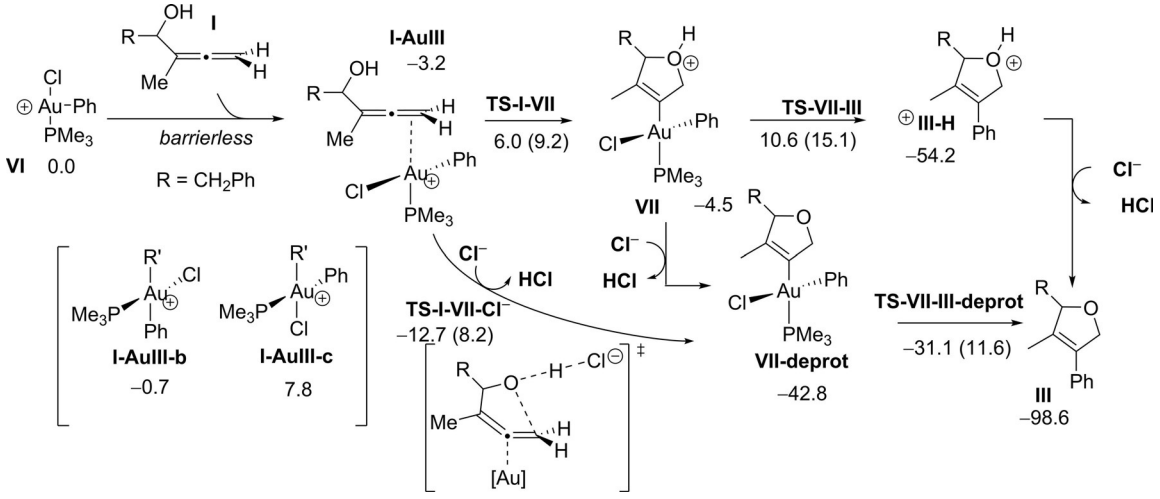
$$\Delta G^{\ddagger} = \frac{(\Delta G^{0} + \lambda)^{2}}{4\lambda}$$

where ΔG^0 is the reaction energy and λ is the reorganization energy (the difference between the energy of the product state with its equilibrated solvent environment and its energy with the geometry and solvent environment of the reactant state).

We propose that the SET occurs on a van der Waals complex (see the Supporting Information) where the phenyl group attached to the gold center is stacked on one of the bipyridine rings on the ruthenium complex, so that reactant and product states simply involve the structure of this complex before and after the electron transfer from ruthenium to gold has occurred; a triplet Ru(III)-Au(II) complex in the former case, and a singlet Ru(II)-Au(III) complex in the latter. Analysis of the spin density of both structures confirms the proposed electron distribution (see the Supporting Information). With a ΔG^0 of -23.3 kcal mol^{-1}, and a λ of 24.0 kcal mol^{-1}, the resultant activation energy for the SET to intermediate **V** is essentially barrierless (0.1 kcal mol^{-1}). Thus, we consider that it is likely that the oxidation takes place on the Au(I) complex, before it has been coordinated to the allenol, and that the cyclization of the allenol fragment and its coupling with the phenyl group is catalyzed by a gold(III) complex. Scheme 11 displays the mechanism proposed for such a transformation. We have chosen **1a**, as model allenol **I** since it combines a structure simple enough to make it computationally affordable and a very good yield of the coupled product (77%).

Taking **VI** and **I** as the reference for energy, we find that the complexation is favored by 3.2 kcal mol^{-1}. The resultant tetracoordinated Au(III) complex adopts a square planar geometry where the allene is *trans* to the phosphine ligand; this arrangement is significantly lower in energy than its isomers. As a result, we will only study the evolution of this isomer of **I-AuIII**. This coordination step is deemed to be barrierless, as constrained geometry optimizations at increasing Au-allene distances (see the Supporting Information) result in steadily increasing energy values.

In the way from separate reactants to **III**, a proton needs to be lost from the oxygen at some point. We have proposed its capture by Cl^- in our estimation of the associated reaction energies, but other bases could be used for this. One alternative could involve the deprotonation of **I-AuIII**, leading to a stronger nucleophile for the cyclization step. However, all our attempts to computationally characterize the product of such a reaction led to the fragmentation of anionic **I-AuIII** into an aldehyde and a gold-coordinated alkyne, which would prevent the reactivity of interest. Thus, we propose that the alcohol attacks the activated allene, leading to gold-dihydrofuran **VII** through a barrier of 9.2 kcal mol^{-1}. **VII** would then be deprotonated before undergoing a reductive elimination that leads to the coupling product **III** and regeneration of the original gold(I) catalyst, through a barrier of just 11.6 kcal mol^{-1}. This reductive elimination, a very ex-



Scheme 11. Proposed mechanism for the reaction of allenol **I** with Au(III) complex **VI**. Relative Gibbs free energy values in kcal mol^{-1} are given for each structure, using **VI**+**I** as a reference. Activation free energies for the transition states indicated in the Scheme are noted between parentheses.

ergonic reaction, can also proceed directly from protonated **VII**, albeit with a somewhat larger barrier of 15.1 kcal mol^{-1}, leading to **III-H$^+$**, which can then lose a proton to become product **III**.

The formation of **VII-deprot** can also be achieved in one step with the assistance of the base on the cyclization transition state, in a process significantly more favorable (with a barrier of 8.2 kcal mol^{-1} with respect to the chloride coordinated **I-AuIII**).

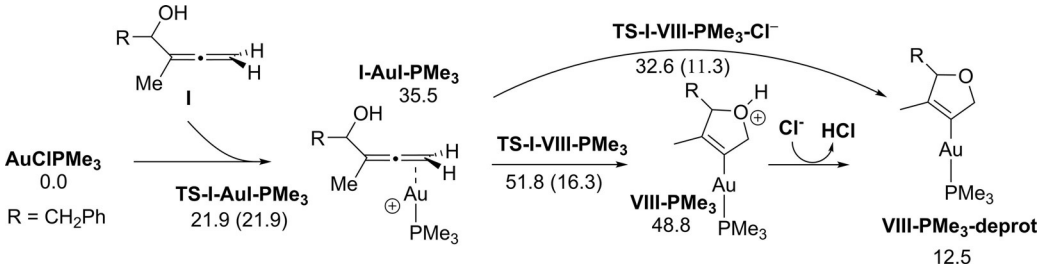
Should the order of steps be reversed, the reaction mechanism would start with coordination of allene **I** to AuClPMe$_3$, with displacement of one of the ligands, as depicted in Scheme 12. We are presenting here the cationic paths resulting from the formation of the **I-AuI-PMe$_3$** complex, generally accepted for this kind of cycle, but the equivalent paths with the neutral chloride complex can be found in the Supporting Information. Similarly to the Au(III)-catalyzed cyclization, a stepwise path involving nucleophilic attack of the hydroxy group, followed by deprotonation of intermediate **VIII-PMe$_3$** could also be invoked. However, even though the reaction barrier is accessible, it is considerably higher than the concerted cyclization-deprotonation mechanism (**TS-I-VIII-PMe$_3$-Cl$^-$**), which becomes the preferred alternative.

After the formation of **VIII-deprot**, a first oxidation of the Au(I) center to Au(II) can proceed through incorporation of a phenyl radical to the metal coordination sphere, followed by further oxidation to Au(III) *via* a SET from the Ru(bipy)$_3$ complex (see Scheme 13). The first step of this transformation was also found to be barrierless.

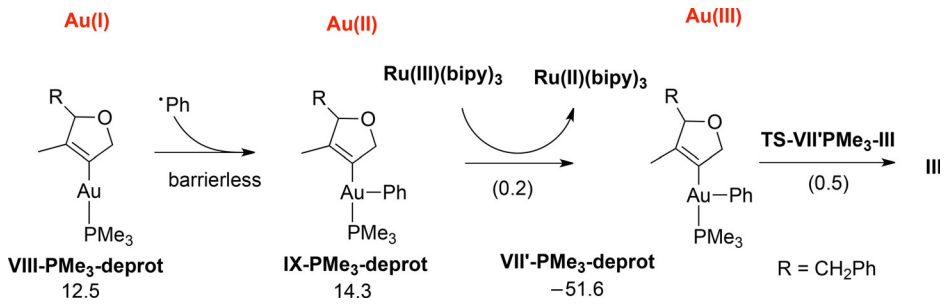
For estimating the barrier for the SET from ruthenium to gold in **IX**, we have followed the same protocol as previously described: using a van der Waals complex as the framework where the single electron transfer takes place.

Starting from tricoordinated structures **IX-PMe$_3$-deprot** (see Scheme 13), we find that the electron transfer is very easy, with a barrier of 0.2 kcal mol^{-1}. The low barrier found for the subsequent reductive elimination on complex **VII′-PMe$_3$-deprot**, 0.5 kcal mol^{-1}, suggests that product **III** would be formed directly from this Au(III) tricoordinated complex, instead of visiting tetracoordinated **VII-deprot** (see Scheme 11).[22]

Thus, we have found that the activation of the allene towards the intramolecular nucleophilic attack of the alcohol is more efficient with the Au(III) than with the Au(I) complex (with barriers around 10 kcal mol^{-1} *vs.* 14–19 kcal mol^{-1} for the latter). Our application of Marcus theory to the SET between Ru(bipy)$_3$ and the Au(II) complex, leads to a barrierless process in the case of **V**, and also in **IX-PMe$_3$**, making this step very fast in both paths. This would point at the catalyst oxidation-cyclization as the favored mecha-



Scheme 12. Coordination of AuClPMe$_3$ to allenol **I** and subsequent cyclization. Relative Gibbs free energy values in kcal mol^{-1} are given for each structure, using **AuClPMe$_3$+I** as a reference. Activation free energies for the transition states indicated in the Scheme are noted between parentheses.



Scheme 13. Oxidation of Au(I) to Au(III) on the cyclic system. Gibbs free energy values (in kcal mol^{-1}) are calculated relative to AuClPMe$_3$ and allenol **I**. Activation free energies are given between parentheses. The estimation of the relative free energies of **VII′**, has been calculated adding the free energy corresponding to the SET step on the gold-Rubipy complexes to the free energies of structures **IX**, not taking into account any (*de*)complexation energy.

nism. However, the intervention of an auxiliary base that deprotonates the alcohol in concert with the formation of the C–O bond, can lower these barriers up to the point where they are made irrelevant, making these two paths competitive. In this case, it is the coordination of the gold center to the allene group that can determine the preference for one path or the other. The activation barriers found for the exchange of a chloride or phosphine ligand for allenol **I** on Au(I) complex $AuClPMe_3$, which are around 21 kcal mol^{-1} (see Scheme 12), are high in comparison with the other steps along the mechanism [and with the barrierless process found for the coordination of **I** to Au(III) complex **VI**] also setting the oxidation-cyclization path as the preferred option.

Conclusions

In conclusion, a light-driven direct method for the allene cycloetherification/arylation cascade with diazonium salts using dual gold and photoredox catalysis to circumvent traditional limitations has been developed. The final products, 2,3,4-trisubstituted-2,5-dihydrofurans, have been obtained in a totally controlled manner in good yields.[23] DFT calculations revealed that the mechanism of this transformation involves an initial oxidation of Au(I) to Au(II) through incorporation of an aryl radical, followed by an SET from $Ru(bipy)_3$ which leads to an Au(III) complex. It is the latter species which catalyzes the cyclization of the allenol and the subsequent reductive elimination to yield the coupling product. Although a mechanism where the sequence of the oxidation-cyclization steps is inverted is feasible, the relatively high activation barrier for the coordination of the allene to the Au(I) species makes it non-competitive.[24]

Experimental Section

General Methods

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, or a Bruker Avance-300 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^1H, 7.27 ppm; ^{13}C, 76.9 ppm), or C_6D_6 (^1H, 7.16 ppm; ^{13}C, 128.0 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg $cm^2 g^{-1}$ at 20 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. Flash chromatography was performed by using silica gel 60 (230–400 mesh). Products were identified by TLC (silica gel). UV light (λ = 254 nm) and a solution of phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) were used to develop the plates.

α-Allenols **1a–f**, **5a–e, (+)-7d**, and **(+)-7e** were prepared adopting our previously described procedure.[25] α-Allenols **1g–i** and **7a–c** were prepared by known literature procedures.[26] Bis(α-allenols) **9a** and **(+)-9b** were prepared through our reported method.[16]

General Procedure for the Gold-Photoredox-Cocatalyzed Reaction between Allenols and Diazonium Salts. Preparation of 2,3,4-Trisubstituted-2,5-dihydrofurans 3, 6, 8 and 10

In a flask in the absence of light at −78 °C, $(Ph_3P)AuCl$ (10 mol%) and $[Ru(bpy)_{3l}](PF_6)_2$ (2.5 mol%) were sequentially added to a solution of the corresponding arenediazonium salt **2** (3.0 equiv.) and the appropriate allenol **1** (1.0 mmol) in a mixture of MeOH/MeCN (3:1, 7.5 mL). The reaction mixture was then warmed to room temperature and stirred under irradiation from a visible light source (21 W fluorescent light bulb installed in a tool box). After completion (TLC), diethyl ether was added and the mixture was filtered through a pad of silica gel. The solvent of the filtrate was removed under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **3**, **6**, **8** and **10** are given in the Supporting Information.[27]

3-Aryl-2,5-dihydrofuran (3aa): From 49 mg (0.28 mmol) of allenol **1a**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent, gave compound **3aa** as a yellow oil; yield: 54 mg (77%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.23 (m, 10 H), 5.06 (m, 1 H), 4.84 and 4.67 (m, each 1 H), 3.07 (dd, J = 14.0, 3.9 Hz, 1 H), 2.81 (dd, J = 14.0, 6.6 Hz, 1 H), 1.84 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 138.1, 133.8, 132.0, 131.9, 129.5 (2 C), 128.3 (2 C), 128.0 (2 C), 127.4 (2 C), 127.1, 126.1, 90.9, 76.9, 40.6, 11.6; IR (CH_2Cl_2): ν = 1602, 1140 cm^{-1}; HR-MS (ES): m/z = 251.1419, calcd. for $C_{18}H_{19}O$ $[M+H]^+$: 251.1436.

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[22] Although we have not calculated the barrier associated to the incorporation of a fourth ligand (either chloride or phosphine) to complete the coordination sphere of the gold center, we have found that tetracoordinated species **IX** are more stable than the corresponding tricoordinated compounds (see the Supporting Information). After oxidation, these paths would converge with those described in Scheme 11, where a facile reductive elimination is expected on **VII-deprot**.

[23] Concerning the mass balance, the unproductive starting allenol gives rise to non-arylated dihydrofurans or unidentified side products, while the excess of diazonium salt formed 1,2-diaryldiazenes.

[24] We have assumed that tricoordinated **VI** is the start of the first path, because of the preferred tricoordination of the Au(II) compounds studied and the fast SET on them. Once **VI** is formed it can be also expected that it will easily coordinate with the acetonitrile used as solvent, making necessary the consideration of an extra step in this mechanism. This step would involve the exchange of acetonitrile with allene **I** in the coordination sphere of gold(III). Even if this is the case, the activation barrier for such a process has been calculated to be considerably lower than those found for the ligand exchanges on the Au(I) complexes (15.3 kcal mol^{-1} for a model allene, 1-phenylbuta-2,3-dien-2-ol).

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[27] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains compound characterization data, experimental procedures, and copies of NMR spectra for all new compounds.

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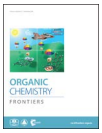

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Transition metal-free controlled synthesis of bis[(trifluoromethyl)sulfonyl]ethyl-decorated heterocycles†‡

Pedro Almendros,[a] Hikaru Yanai,[b] Shoki Hoshikawa,[b] Cristina Aragoncillo,[c] Carlos Lázaro-Milla,[c] Mireia Toledano-Pinedo,[c] Takashi Matsumoto*[b] and Benito Alcaide*[c]

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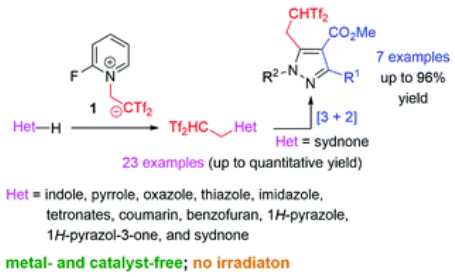
Abstract

Several heterocycles reacted with shelf-stable 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl] ethan-1-ide, a latent $Tf_2C{=}CH_2$ source, to give rise in a mild and controllable way to adducts *via* direct C–H bis[(trifluoromethyl)sulfonyl]ethylation reactions. This metal- and irradiation-free protocol is convenient. Besides, the volatile side-product 2-fluoropyridine can be smoothly eliminated under vacuum, which facilitates purification. The substrate scope survey discloses that exquisite chemo- and regioselectivities are achieved in a variety of heterocyclic systems. Of particular interest are the late-stage structural modification of known pharmaceuticals, such as the marketed drugs Phenazone (Antipyrine) and Edaravone, and the development of a water soluble fluorescent dye.



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